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OFF-LABEL USE, PRESCRIPTION, AND MARKETING OF FDA-APPROVED DRUGS: AN ASSESSMENT OF LEGISLATIVE AND REGULATORY POLICY

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I. INTRODUCTION

Pharmaceutical legislation and regulation in the United States are recent phenomena. Indeed, before the early part of the twentieth century, the industry was entirely free of external controls.[1] Congress first enacted legislation with the Pure Food and Drug Act of 1906,[2] which focused on the purity and quality of products and the accuracy of their branding.[3] Legal control over the efficacy and safety of drugs was strengthened substantially through the Federal Food, Drug and Cosmetic Act of 1938,[4] the antecedent of the existing FDA drug approval process. The rigor of external controls was expanded again with the passage of the Drug Amendments of 1962,[5] which created the phases of clinical testing presently required for the approval and marketing of new drugs.[6] Thus over a period of less than 60 years, the pharmaceuticals market has been transformed to a closely regulated environment. As the FDA developed and grew through the 1970s,[7] the bureaucratization of rule over the drug industry expanded apace.[8]

In contrast, the 1980s and 1990s have brought a retrenchment from the trend of escalating administrative requirements in pharmaceuticals marketing. The deregulatory period of the Reagan administration[9] brought

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1. *See* Eric Lindemann, *Importing AIDS Drugs: Food and Drug Administration Policy and its Limitations*, 28 GEO. WASH. J. INT'L L. & ECON. 133, 133 (1994) (dating federal regulation of pharmaceutical industry to the first decade of the twentieth century).

2. Pure Food and Drug Act of 1906, ch. 3915, 34 Stat. 768 (repealed 1938).

3. *See id.* §§ 1-12, 34 Stat. at 768-72.

4. Pub. L. No. 52-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-392 (1997)).

5. Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C. §§ 301-381 (1997)).

6. *See id.*

7. *See* United States v. Parkinson, 240 F.2d 918, 921 (9th Cir. 1956) (observing the "tendency of executive agencies to expand their field of operations").

8. This trend was so extreme that one commentator refers to the traditional FDA approval process, developed in the Kefauver-Harris Amendments, as "bureaucratic arteriosclerosis." *See* PHILIP K. HOWARD, THE DEATH OF COMMON SENSE: HOW LAW IS SUFFOCATING AMERICA 84 (1994) (quoting Louis Jaffe).

9. *See* Michael C. Dorf & Charles F. Sabel, *A Constitution of Democratic Experimentalism*, 98 COLUM. L. REV. 267, 361 (1998) (associating the Reagan administration with an era of deregulation).

changes to the prescription drug industry,[10] largely triggered by activists' demands for expedited marketing of new HIV and AIDS treatments.[11] These two decades have been a time of intense reform in the areas of pharmaceutical legislation and regulation.[12]

Many of the components of this era of change have taken the form of what I have labeled "liberalizations"—movements toward increased consumer access to drugs and related products, and expanded freedom in the manufacture and marketing of those products.[13] Early AIDS-era reforms[14] included the development of such processes as use of investigational new drugs for treatment,[15] fast-track approvals,[16] parallel-track investigational new drugs,[17] and drug approvals based on surrogate marker data.[18] In addition, Congress passed the Dietary Supplement Health and Education Act of 1994,[19] which further deregulated the already loosely governed market for dietary supplements.[20] More recently, regulatory and legislative liberalizations have focused on the increasingly complex issue of pharmaceutical marketing.[21]

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10. *See* Jeffrey D. Winchester, Note, *Section 8(c) of the Proposed Restatement (Third) of Torts: Is It Really What the Doctor Ordered?*, 82 CORNELL L. REV. 644, 681 (1997) (observing "recent political emphasis on a 'laissez faire' approach to agency regulation of the pharmaceutical industry").

11. *See* Phillip J. Hilts, *How the AIDS Crisis Made Drug Regulators Speed Up*, N.Y. TIMES, Sept. 24, 1989, at E5 (noting the connection between AIDS activism and FDA reforms).

12. *See* Note, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009 (1995) (discussing this recent deregulation of the pharmaceutical industry, as well as present and future initiatives).

13. *See* Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. (forthcoming 1999).

14. *See* Jeff Nesmith, *Recall Raises Questions Over Speed of FDA Drug Approvals*, COX NEWS SERVICE, June 23, 1998, *available in* LEXIS, News Library, Allnws File. While these reforms can be traced to the efforts of HIV and AIDS activists who sought easier access to new treatments in the 1980s, they are also said to result from aggressive lobbying by the pharmaceutical industry during the same period. *See id.*

15. *See* 21 C.F.R. § 312.1 (1998).

16. *See* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations: Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41,516 (1988).

17. *See* 57 Fed. Reg. 13,250, 13,257-58 (1992).

18. *See* 57 Fed. Reg. 58,942 (1992).

19. Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified as amended in scattered sections of 21 U.S.C.).

20. *See* Margaret Gilhooley, *Herbal Remedies and Dietary Supplements: The Boundaries of Drug Claims and Freedom of Choice*, 49 FLA. L. REV. 663, 679-706 (1997) (examining these changes).

21. This increasing complexity is due largely to the role of the Internet as a source of information, and questions that arise concerning whether and when posting data on the Internet comprises marketing efforts. This challenge has led the FDA to consider issuing general guidance

For example, the Food and Drug Administration (FDA) has initiated changes over the past few years that have dramatically broadened the ways in which drug manufacturers advertise pharmaceutical products directly to consumers.[22] Today, pharmaceutical companies place ads on television, radio and the Internet, for the first time directly informing patients about the purposes, functions, and advantages of various prescription drug products.[23] Although the FDA continues to fight what it regards as abusive practices,[24] its general tendency during the past two decades has been toward relaxation rather than enhanced control.[25]

This recent regulatory movement in the direction of expanded marketing discretion has been matched by a parallel federal legislative initiative. In 1997, Congress enacted the Food and Drug Administration Modernization Act of 1997 (Modernization Act),[26] the first major congressional legislation in the area of pharmaceutical law in recent years. While the law is comprehensive, covering a wide range of subjects related

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on Internet use in this regard. *See* Jill Wechsler, *Communications Slowdown*, PHARM. EXEC., July 1997, at 20.

In regard to FDA restrictions on the advertising of drug products, either to professionals or to the public, interactive computer technology raises difficult and intriguing new questions. For example, when a drug manufacturer includes information and links on its home page, at what point does the information contained or cross-linked qualify as marketing of products and particular uses of products? Are the drug companies reaching out to the public in a form of advertisement, or are they simply providing them with a resource they can examine at their own initiation? The FDA began examining these complex issues during a two-day conference it held in October of 1996. *See* James G. Dickinson, *No Washington Cheer for Drug Manufacturers in 1997*, MED. MKTG. & MEDIA, Dec. 1996, at 12.

The challenges of these issues are further complicated by the need for investigators and manufacturers to communicate, the utility of the Internet in facilitating these communications, and the access that consumers have to much information shared over the Internet. For discussion of these aspects of the problem, see Marilyn A. Moberg et al., *Surfing the Net in Shallow Waters: Product Liability Concerns and Advertising on the Internet*, 53 FOOD & DRUG L.J. 213, 221-22 (1998) (discussing these issues); *see also* Marc J. Scheineson, *Legal Overview of Likely FDA Regulation of Internet Promotion*, 51 FOOD & DRUG L.J. 697 (1996).

22. *See generally* Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141 (1997).

23. *See* Michael C. Allen, Comment, *Medicine Goes Madison Avenue: An Evaluation of the Effect of Direct-to-Consumer Pharmaceutical Advertising on the Learned Intermediary Doctrine*, 20 CAMPBELL L. REV. 113, 115 (1997).

24. *See, e.g.*, Natalie Hopkinson, *FDA Delays Rules Aimed at Curbing Drug Promotions*, WALL ST. J., July 20, 1998, at B8 (concerning possible prospective FDA efforts to prohibit drug manufacturers that purchase pharmacy benefit management companies from using the latters' patient lists for marketing mailings).

25. *See* Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access*, 11 YALE J. ON REG. 401, 410-18 (1994) (describing relaxed FDA control during this period).

26. 21 U.S.C. § 301 (1997).

to both drugs and medical devices,[27] some particular provisions have the potential to alter substantially the ways in which pharmaceuticals are marketed in the United States.

This Article focuses on one such provision of the Modernization Act—the limited authorization, for the first time, of "off-label" marketing of drugs. The Article describes and critiques various off-label practices, in order to provide an assessment of present policies and recommendations for future legislative and regulatory initiatives.

Specifically, Part II explains what off-label use, prescription, marketing, and promotion entail. It then examines the arguments for legalization made by proponents of off-label practices, as well as the arguments against legalization made by opponents of off-label practices. Part III describes the major provisions of the Modernization Act that liberalize off-label processes. Part IV is an effort to resolve the conflicting positions outlined earlier in the Article, by assessing the validity and relative strengths of each position. The Article closes with Part V, which summarizes the major points and propositions.

II. OFF-LABEL USE, PRESCRIPTION, AND MARKETING/PROMOTION OF DRUGS

This Part is divided into three Subparts. The first Subpart briefly defines the term "off-label," explaining the legislative and regulatory context in which the phrase was developed. The second Subpart defines with specificity a number of the terms that employ the modifier "off-label." The third Subpart discusses the controversy over various off-label activities and functions.

A. *Defining "Off-Label"*

The term "off-label" comes by inference from congressional legislation and FDA regulations concerning drug labeling. The Food Drug and Cosmetic Act of 1938 first required drug companies to label pharmaceutical products with various directions and warnings.[28] Detailed

27. In addition to the off-label marketing portions of the statute that are directly addressed in this article, sections of the legislation concern user fees that finance expedited FDA review, pediatric drug studies, fast-track studies and approvals, streamlining of clinical research, pilot and small scale manufacture of drugs, exemptions for investigational devices, and food regulation improvements, among others. *See id.*

28. *See* Federal Food, Drug and Cosmetic Act, ch. 675, § 502(f), 52 Stat. 1040, 1051 (1938) (codified as amended at 21 U.S.C. §§ 301-392 (1997)). Labeling requirements have developed and changed over the intervening period. Most importantly, distinctions have been made between over-the-counter drugs, which are labeled with directions and warnings directed to the consumer, and prescription drugs, which are labeled for only the physician, who serves as "learned intermediary" between the pharmaceutical manufacturer and the patient. *See id.*; *see also* Charles J. Walsh et al.,

regulations tell manufacturers what must be included in a drug's label, including things like information necessary for safe and effective use,[29] as well as warnings, precautions, clinical pharmacology, indications, contraindications, and adverse reactions.[30] The regulations are intended to ensure that the drugs and their promotional literature contain accurate and complete information regarding approved use and risks.[31] Although the ultimate goal is consumer protection, prescription drug labels today are aimed at physicians, who have held a longstanding position in American jurisprudence as "learned intermediaries" between manufacturers and users.[32] FDA-approved labeling is included not only as a product insert, but also as an entry in the *Physician's Desk Reference.*[33]

When the agency approves a new drug, it does so for specific purposes associated with the clinical trial findings that supported the drug's application. Logic tells us that, since the universe of possible unapproved uses is infinite, it would be difficult for the FDA to promulgate labeling requirements for all uses beyond those for which the drug was approved.[34] Accordingly, pharmaceutical companies are required to convey, in the drug's formal labeling, information regarding only those uses for which the drug was approved.[35]

By inference, all other uses therefore have come to be designated as "off-label" uses.[36] If a manufacturer wishes an off-label use to be added to

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The Learned Intermediary Doctrine: The Correct Prescription for Drug Labeling, 48 RUTGERS L. REV. 821(1996) (discussing this history).

29. *See* 21 C.F.R. § 201.56(a) (1998).

30. *See* 21 C.F.R. § 201.56(d) (1998).

31. *See* Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" from the "Need to Know" about Consumer Product Hazards*, 11 YALE J. ON REG. 293, 326-33 (1994) (discussing the labeling requirements for prescription drugs).

32. *See* Margaret Gilhooley, *Learned Intermediaries, Prescription Drugs, and Patient Information*, 30 ST. LOUIS U. L.J. 633 (1986) (discussing this concept).

33. *See* Edmund Polubinski, III, Note, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 VA. L. REV. 991, 995 (1997) ("The final labeling as approved forms the package insert that accompanies the drug to market and also appears in the *Physician's Desk Reference.*").

34. Of course, a middle ground is possible here. For example, the FDA could promulgate informational requirements not only relating to approved uses, but also foreseeable uses, common unapproved uses, etc. Nonetheless, it remains true that it would be logistically impossible for the FDA to require information be given on all unapproved uses, since the range of such uses has no limits.

35. *See* David W. Opderbeck, *How Should FDA Regulate Prescription Drug Promotion on the Internet?*, 53 FOOD & DRUG L.J. 47, 55 (1998) ("[R]egulations prohibit labeling listing 'off-label' uses for which the drug is not indicated.").

36. *See* William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (supplying the following definitional guidance: "Using an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease

a drug's labeling, it must apply to the FDA for approval as it would for a new drug.[37] Accordingly, Professor Merrill has observed that "the manufacturer of a drug with potential multiple uses confronts the prospect of having to surmount the obstacles to FDA approval several times before it can exploit the full market potential of the drug."[38] Of course, inclusion of a new use in the drug's labeling may not increase sales, especially if off-label applications are already well known and off-label use is already widespread.[39] In such instances, companies have little incentive to apply for labeling authorization under tedious and expensive FDA procedures.[40]

B. *Defining Specific Kinds of Off-Label Activities*

This Subpart briefly defines and examines the three basic kinds of off-label activities—off-label use, off-label prescription, and off-label marketing and promotion.

1. Off-Label Use

Off-label use of a prescription drug occurs whenever the consumer of the drug uses it in a manner that varies in some way from the instructions in the drug's labeling, which are limited to FDA-approved uses.[41] Logically, such off-label uses can occur with or without the knowledge or consent of the prescribing physician, and with or without the manufacturer's knowledge or encouragement of the variant use. The most typical off-label uses are use by persons other than those for whom the drug was approved, use in dosages other than the approved dosages, use for conditions other than those indicated in the labeling, and use in unapproved combination with other drugs.[42]

It would be logistically impracticable, although not technically impossible, for Congress or the FDA to ban the off-label use of drugs. This

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but varying from the indicated dosage, regimen, or patient population may all be considered off-label use.").

37. *See* 21 C.F.R. §§ 314.70-.71 (1998).

38. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1853-54 (1996).

39. *See* Kaspar J. Stoffelmayr, *Products Liability and "Off-Label" Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 277 (1996) (observing that adding an off-label use to a label has little effect on sales when doctors already know of the off-label application).

40. *See id.* (noting manufacturers frequently decline to seek approval for off-label uses because of time and expense of FDA procedures).

41. *See* Michael E. Petrella, Comment, *License to Maim: Federal Pre-emption and the Medical Device Amendments of 1976*, 6 HEALTH MATRIX 349, 368 n.122 (1996) (defining off-label uses as those the FDA has not approved as safe or effective).

42. *See* Christopher, *supra* note 36, at 248.

difficulty exists because a deviant use[43] can be accomplished independently by the patient in the privacy of his or her own home, without the assistance of medical practitioners or any other professionals.[44] Once a prescription drug is in a patient's hands, the manner in which the drug is used also is in the patient's hands. Perhaps due in part to these dynamics,[45] off-label use of prescription drugs was not outlawed even prior to the legislation passed in 1997, which liberalized the marketing of such use.[46]

2. Off-Label Prescription

Off-label prescription of drugs occurs when a doctor prescribes a drug in any manner that varies from labeling specifications.[47] A doctor who prescribes a drug that has been approved by the FDA for purpose X, in order to achieve the different purpose Y, is prescribing off-label.[48] The term also applies to prescription of a drug to groups other than those for whom the FDA approved it,[49] for periods of use exceeding the labeled recommended use,[50] or in combination with other FDA-approved drugs.[51]

Legislators and regulators could prohibit off-label prescription of drugs at least somewhat more effectively than they could prohibit off-label use

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43. "Deviant use" refers here to the deviation of a use from labeling specifications. The term is not intended to be pejorative, or to impute culpability of any kind to the user.

44. Off-label use certainly could be prohibited, just as the use of illegal drugs such as marijuana is prohibited. Given how difficult it is for law enforcement agencies to expunge the use of contraband in the privacy of a user's home, imagine how difficult it would be for law enforcers to expunge the unauthorized misuse of legally prescribed drugs in the privacy of a user's home. The law certainly could be passed, but the implementation and enforcement of the law would be virtually impossible.

45. *See* Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PROD. & TOXICS LIAB. 139, 139 (1994) (discussing pragmatic difficulties in controlling off-label uses).

46. *See* FDA Modernization Act of 1997, 21 U.S.C. § 301 (1997).

47. *See* Michael I. Krauss, Essay, *Loosening the FDA's Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare*, 4 GEO. MASON L. REV. 457, 470 (1996) (referring to off-label prescription as physicians' prescribing drugs for uses other than FDA approved uses).

48. *See* Timothy R. Franson, *FDA Rules Can Cost Lives*, USA TODAY, Oct. 26, 1995, at 12A (discussing prescription of drugs approved for one disease in the treatment of a different disease).

49. Perhaps the most common off-label prescription occurs when drugs approved for treatment of adults are prescribed to treat children. *See* Charles J. Cote et al., *Is the "Therapeutic Orphan" About to Be Adopted?*, 98 PEDIATRICS 118, 122 (1996) (discussing this off-label use).

50. *See, e.g.*, Jeff Nesmith, *Drug Recall Puts Shadow on Approval Process*, ATLANTA J. & CONST., June 24, 1998, at A03 (discussing physician prescription of drug Duract, prior to its recall, for periods exceeding the labeled 10-day limit).

51. *See, e.g.*, John Accola, *"Fen-Phen" Foes Fuming Over Proposed FDA Review Change*, ROCKY MTN. NEWS, Sept. 30, 1997, at 4B. The administration of fenfluramine in tandem with phentermine, prior to the recall of the former, was a popular off-label prescription during the middle years of this decade.

of drugs. Doctors keep medical records that indicate diagnoses, and laws could be passed to ensure that a prescribed drug has been approved for the diagnosed condition. Of course, logistical problems, such as doctors' circumventing the law by misrecording diagnoses in medical records, could not be entirely eliminated. Presumably, however, risk of exposure and punishment would be a reasonably strong deterrent to such professional lapses. Accordingly, a ban on off-label prescriptions likely would be more feasible than a ban on off-label use. Logic also tells us that such a ban, although not a direct prohibition of off-label use, probably would serve to reduce its incidence.[52]

Nevertheless, off-label prescription was permissible before Congress's 1997 liberalizations.[53] This fact is largely attributable to the scope of the FDA's authority, which extends to manufacturers of drugs but not to the physicians who dispense them.[54] Doctors long have been judicially accorded broad and unconstrained prescribing authority.[55] Numerous decisions support this approach, which emphasizes physician autonomy and discretion within an otherwise rigorous regulatory environment.[56]

The latitude accorded the medical profession in regard to off-label prescription is extensive. For example, doctors generally need not tell patients that the drugs they are taking have not been approved for the prescribed use.[57] Failure to inform patients that the treatment they are receiving is an off-label application does not, in itself, constitute malpractice.[58] Of course, physicians can be held liable for negligence if their off-label applications are sufficiently careless, imprudent, or unprofessional.[59] Conversely, they also face the risk of liability for failing

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52. There are two reasons why prohibiting off-label prescriptions would likely reduce the incidence of off-label use. First, patients would have greater trouble getting access to drugs that doctors were not legally permitted to dispense for the patients' symptoms. Second, patients would be less likely even to know of a potential off-label use if doctors were discouraged from off-label prescribing. In many instances, the patient who uses a drug product off-label is directed to do so by a doctor who has explained and encouraged the use.

53. *See* James L.J. Nuzzo, M.D., *Independent Prescribing Authority of Advanced Practice Nurses: A Threat to the Public Health?*, 53 FOOD & DRUG L.J. 35, 45 (1998) (noting 1982 FDA statement that off-label prescribing is an "accepted medical practice" that the agency condones).

54. *See* Althea Gregory, *Denying Protection to Those Most in Need: The FDA's Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI. & TECH. 121 (1997).

55. *See* Drusilla S. Raiford et al., *Determining Appropriate Reimbursement for Prescription Drugs: Off-Label Uses and Investigational Therapies*, 49 FOOD & DRUG L.J. 37, 39 (1994).

56. *See, e.g.*, Rhone-Poulenc Rorer Pharm., Inc. v. Marion Merrell Dow, Inc., 93 F.3d 511, 514 n.3 (8th Cir. 1996); Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir. 1989); United States v. Evers, 453 F. Supp. 1141, 1149-50 (M.D. Ala. 1978), *aff'd*, 643 F.2d 1043 (5th Cir. 1981).

57. *See* Joan R. Rose, *Informed Consent: How Much Must Doctors Reveal?*, MED. ECON., Apr. 29, 1996, at 25.

58. *See id.*

59. *See* AM. ACAD. PEDIATRICS COMMITTEE ON DRUGS, *Unapproved Uses of Approved*

to provide appropriate treatment simply because it is an off-label application.[60] Regardless of whether a physician is deciding to prescribe or withhold an off-label treatment, the failure to exercise reasonable care opens channels of potential liability, just as it would in any other area of medical practice.[61]

3. Off-Label Promotion and Marketing

Finally, compare off-label use and prescription with off-label promotion and marketing of drugs. The latter processes occur when the manufacturers of the drugs promote or advertise their products for purposes, to users, in dosages, or in combinations other than the FDA-approved ones.[62] As this definition suggests, the term "off-label marketing" applies only to activities of manufacturers. Accordingly, when physicians write freely about off-label applications of prescription drugs, they are not engaging in off-label marketing, and their activities never have been proscribed.[63] Conversely, if the manufacturer of these drugs reproduces or distributes the doctor's writings to other physicians, its activities are considered to fall in what historically has been the highly-controlled arena of off-label marketing.[64]

While direct and blatant advertising to physicians is easily identified as off-label marketing, other practices fall in gray areas. For example, a 1997 FDA release suggested that manufacturers could be engaging in off-label promotion when they provide grants supporting symposia on unapproved uses of drugs,[65] or grants to managed care organizations to encourage their

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Drugs: The Physician, the Package Insert, and the Food and Drug Administration: Subject Review, 98 PEDIATRICS 143, 144 (1996).

60. *See id.* ("Indeed, a physician could be subject to a claim of malpractice if he or she denied a patient potentially the best treatment solely because the use was not included in the official labeling of the drug.").

61. For discussion of the reasonable care test in malpractice cases, see Susan Cowan Atkinson, Note, *Medicare "Cost Containment" and Home Health Care: Potential Liability for Physicians and Hospitals*, 21 GA. L. REV. 901, 913-17 (1987).

62. A broad definition of off-label marketing and promotion would include these functions directed at anyone, including both health care professionals and consumers. As explained in Section III, the 1997 legislation that permits off-label advertising and promotion restricts these processes to be directed to certain qualified professionals. *See* 21 U.S.C. § 360aaa(a) (1997). Accordingly, when I speak of authorized off-label marketing and promotion, I am restricting my reference to only those professional groups to whom manufacturers can direct their promotional literature under the statute.

63. *See* Richard A. Samp, *FDA Censorship Threatens Patient Medical Care*, CONSUMERS' RES. MAG., Dec. 1994, at 16.

64. *See id.*

65. *See* 62 Fed. Reg. 64,074 (1997). The test for whether such support is off-label marketing has generally centered around the issue of independence: "If a scientific or educational program that pertains to research concerning potential new uses of a medical product is intended to be and is

off-label use or promotion of a product.[66]

As described in Part III, off-label marketing and promotion were not permitted before 1997, but were authorized under limited conditions by the Modernization Act, which was passed that year.[67] The ban on off-label promotion and marketing that existed before 1997 was easily implemented because of two factors: ease of infraction identification and ease of enforcement.[68]

The observations in this and the preceding two subsections suggest that off-label use, prescription, and marketing/promotion are processes that can differ substantially in both their capacity to be monitored and controlled and Congress's desire to monitor and control them. Accordingly, the three classes of off-label activities will be discussed in this article using the specific phrases of (a) "use," (b) "prescription," and (c) "marketing," "promotion," or "advertising," and it is important for the reader to remember the significance of the distinctions. When all processes are to be signified inclusively, the phrases "off-label activities," "off-label applications," and "off-label functions" will be employed.

C. *The Controversy Over Various Off-Label Activities and Functions*

We noted in Subpart II.B.1. that off-label use of drugs is virtually impossible to control by law. Off-label prescription, however, could be prohibited with some success, and off-label marketing and promotion are highly susceptible to legislative and regulatory control. The debate over off-label processes and functions has tended to focus mostly on the marketing and promotional aspects that are conducive to legal monitoring. This Subpart examines separately the arguments favoring and disfavoring all off-label processes, with particular emphasis on marketing and promotion functions.

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truly independent of any direct or indirect influence by the sponsoring company," then sponsorship has not been viewed by the FDA as off-label marketing. I. Scott Bass et al., *Off-Label Promotion: Is FDA's Final Guidance on Industry-Supported Scientific and Educational Programs Enforceable?*, 53 FOOD & DRUG L.J. 193, 195 (1998). Conversely, when the sponsoring company seeks to exert influence, it is not considered to be acting independently, and the FDA has viewed its activities as a form of off-label marketing. *See id.*

66. *See* Paul E. Kalb & I. Scott Bass, *Government Investigations in the Pharmaceutical Industry: Off-label Promotion, Fraud and Abuse, and False Claims*, 53 FOOD & DRUG L.J. 63, 67 (1998) (referring to 62 Fed. Reg. 64,074 (Dec. 3, 1997)).

67. *See infra* Part III.

68. Because marketing efforts usually are visible, they usually are also easy to detect. Companies obviously know this and are reluctant to commit blatant, highly observable violations within the tightly controlled and heavily monitored regulatory environment of the drug industry. These dynamics combine to make a ban on off-label marketing not only easy to implement, but to a large extent, self-enforcing.

1. Arguments Favoring Off-Label Processes

Proponents of off-label processes focus predominantly on their potential to expedite the development and availability of effective new treatments. As already noted, physicians traditionally have been permitted to prescribe drugs at their discretion for off-label uses.[69] Subpart II.C.1.a. notes the prevalence of off-label practices in medicine today, and the contention of proponents that these practices contribute immeasurably to the quality of medical care. Subpart II.C.1.b. examines the theoretical foundations for some of the observations in Subpart II.C.1.a., explaining why off-label activities logically should improve the practice of medicine.

a. Contentions that Off-Label Practices Are Both Prevalent and Necessary

Off-label practices are both widespread and beneficial to today's medical practice. Professor Beales contends that off-label uses are frequently "an important part of medical therapy."[70] Page notes that "a significant portion of drug use" today is off-label drug use.[71] One estimate suggests that between twenty and sixty percent of all prescriptions are for off-label uses.[72] Pediatric prescriptions are especially likely to be off-label because many drugs are not tested for use by children.[73]

Other specific examples abound. A report in the *Journal of the National Cancer Institute* states that off-label use of cancer drugs is prevalent.[74] Off-label applications not only are common in cancer therapy; they also are considered to be among the most effective treatments. Off-label applications in oncology have been called "the hallmark of state-of-the-art treatment."[75] Accordingly, proponents often cite the high incidence and effectiveness of off-label cancer drugs to support their position.[76]

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69. *See supra* notes 53-56 and accompanying text.

70. J. Howard Beales, III, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 SETON HALL L. REV. 1370, 1385 (1994).

71. Martin Page, *CBER Status On Reform Initiatives: Industry Reactions and Comments*, 52 FOOD & DRUG L.J. 193, 195 (1997).

72. *See* Krauss, *supra* note 47, at 472.

73. *See* Lisa Schiff, *MSA, AWP and Partner Skirmishes*, BUS. & HEALTH, Sept. 1997, at 89.

74. *See* Kate Nagy, *States Aim Laws at Off-Label Reimbursement*, 85 J. NAT'L CANCER INST. 701, 701 (1993).

75. Gail Dutton, *Should You Let the FDA Decide What Drugs You Pay For?*, BUS. & HEALTH, Oct. 1996, at 65.

76. *See* James G. Dickinson, *FDA Reform Effort Becomes a Dance of Strategy and Tactic*, MED. MKTG. & MEDIA, May 1996, at 12 (calling frequently prescribed off-label cancer drugs "a key example used by the [FDA's] . . . critics when pushing for reforms in the area of unapproved uses promotion").

Off-label prescriptions likewise dominate a number of other areas of medical practice. For example, the great majority of drugs prescribed for the healing of wounds are approved and labeled only for other conditions.[77] Yet perhaps nowhere else has the impact of off-label use been as dramatic as in the treatment of AIDS. Experts suggest that between ninety and one hundred percent of applications, including all of the revolutionary antiretroviral combination therapies,[78] are off-label.[79]

Attorneys Beck and Azari summarize the situation, describing off-label activity as widespread and suggesting it is an essential component of optimal patient care.[80] Indeed, the only factors constraining physicians' off-label prescriptions are potential tort liability[81] and gradually dwindling vestiges of insurance company and health plan policies[82] that deny coverage of off-label applications,[83] where such policies are still legal.[84]

If off-label use of drugs can help patients, then off-label marketing may enable the greatest number of potential beneficiaries to receive the treatments best suited to their needs.[85] The example most frequently cited

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77. *See* Martin Wright, *Prescribing "Off-Label" Drugs for Wound Healing Is Common*, DERMATOLOGY TIMES, July 1996, at 35.

78. *See* Ramón A. Torres & Michael Barr, *Impact of Combination Therapy for HIV Infection on Inpatient Census*, 336 NEW ENG. J. MED. 1531, 1532 (1997). These therapies, first introduced into medical practice in 1995, combine two nucleoside analogues with a protease inhibitor. *See id.* The therapies have been widely hailed as a major breakthrough in HIV and AIDS treatment, resulting in substantial reduction in disease progression and mortality. *See, e.g.*, Robert Steinbrook, *Battling HIV on Many Fronts*, 337 NEW ENG. J. MED. 779 (1997) (observing substantial decline in AIDS deaths immediately following the initiation of antiretroviral combination therapies).

79. *See* Kenneth P. Berkowitz et al., *Congress Tries to Bridge the "Label Gap," But Nobody Is Cheering*, MED. MKTG. & MEDIA, Jan. 1998 (citing panel comments of Steven K. Carter that 90% of AIDS drug use is off-label, as the drugs are approved for single-agent uses at end stages of the disease but often used in combination during earlier stages of the disease; and comments of Mark Smith that off-label use of AIDS treatments is "pretty much 100 percent").

80. *See* James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 71 (1998).

81. *See, e.g.*, Paul v. Bochenstein, 482 N.Y.S.2d 870, 871 (App. Div. 1984) (holding doctor liable for malpractice for administering dosages exceeding manufacturer recommendations).

82. *See* Michael F. Conlan, *Unapproved Uses Prove Worrisome*, DRUG TOPICS, Oct. 21, 1996, at 60 (observing that "denial of reimbursement for off-label drugs ha[s] declined significantly as a problem in the past few years," and observing changes in Medicare policy that increase reimbursement of off-label treatments for cancer patients). For discussion of these policies and some of the reasons the insurance industry gives for the policies, see Bill Gradison, *Don't Rush to Mandate Unproven Therapy Coverage*, BEST'S REV., Nov. 1996, at 80.

83. *See* Allison Bell, *Massachusetts Adopts List of Off-Label HIV Treatments*, NAT'L UNDERWRITER, Apr. 29, 1996, at 49 ("Some health plans refuse to reimburse patients for drugs prescribed for off-label uses.").

84. *See* Harris Fleming Jr., *Going Off-Label*, DRUG TOPICS, Apr. 6, 1998, at 57 (discussing laws being passed in numerous states that require insurance companies to cover off-label prescriptions under a variety of conditions).

85. The reasoning behind this proposition is as follows: the historic legalization of both off-

to support this assertion[86] concerns the off-label use of aspirin to reduce the risk of a heart attack. Credible sources have suggested since the 1980s that tens of thousands of heart attacks would have been averted had it been lawful to advertise the benefits of aspirin for this purpose.[87] Thus while legalized off-label use and prescription are a good start, they simply are not enough. Unless promotion is also permitted, valuable and potentially life-saving off-label uses will remain isolated and limited.

Restricting off-label marketing can contribute to sub-optimal patient treatment in another way—by cutting off a valuable potential source of cost-containment. Subjecting all uses of a drug to FDA approval procedures increases the number of clinical trials, thereby also raising manufacturer research and development expenditures.[88] At least some of these costs will become social costs,[89] as they are passed to consumers in the form of price increases in an environment in which pharmaceutical pricing is already a serious concern.[90]

Another aspect of cost-containment concerns the resources saved or put to better use by the FDA when off-label applications can be marketed without seeking FDA approval. In 1995, House Commerce Committee counsel Alan Slobodin suggested that the FDA expends resources unnecessarily on relatively unimportant side-issues such as the monitoring of off-label uses.[91] Were the FDA to focus on what Slobodin considers its "core mission"[92]—the expedient assessment of new drugs and devices—at least two potential efficiencies might be achieved. Tax dollars spent by the FDA could be reduced, and performance in the core areas could be

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label use and off-label prescription has helped innumerable patients who otherwise would have been denied effective treatment. It is possible, however, that the traditional prohibition of off-label advertising and promotion have thwarted the access of others who may have benefitted from an off-label use, had they only been aware of it.

86. *See, e.g.*, Krauss, *supra* note 47.

87. *See id.* at 471.

88. *See* Beck & Azari, *supra* note 80, at 77.

89. Of course, casting this expenditure as a social cost rather than a social benefit presumes that the resources devoted to the supposedly extraneous research are indeed wasted. If clinical tests of off-label uses were to expose enough risks and dangers of sufficient magnitude, the expense of the tests could be outweighed by the protective functions that they would serve.

90. Earlier this decade, some pharmaceutical companies agreed to curb the rising costs of prescription drugs. *See* Jeffrey H. Birnbaum & Michael Waldholz, *Harsh Medicine: Attack on Drug Prices Opens Clinton's Fight for Health-Care Plan*, WALL ST. J., Feb. 16, 1993, at A1, A6 (noting recommendation of chairman of Merck that drug companies voluntarily limit price increases to inflation rate). Notwithstanding this commitment, prices for some drugs are skyrocketing today. *See* Elyse Tanouye, *Drugs: Behind the Inflation in Prescription-Drug Prices*, WALL ST. J., July 6, 1998, at A17.

91. *See* Jill Wechsler, *Better With FTC?*, PHARM. EXEC., Nov. 1995, at 16.

92. *Id.*

hastened and improved, benefitting consumers and manufacturers alike.[93] The savings could expedite patient access to valuable treatments by permitting the FDA to process new drug applications more quickly using the money it conserves, and by contributing to a reduced public tax burden that would free consumer dollars for spending on pharmaceutical treatments.

b. Theoretical Foundations for the Argument that Off-Label Activities Improve the Practice of Medicine

The preceding Subpart observed that off-label prescription is very common and that proponents suggest that it improves the quality of health care. This Subpart examines the reasoning behind this position. The logic is based on two key realities of the medical and scientific communities: (i) the role of practitioners in the advancement of treatments, and (ii) the need to expedite the distribution of sound scientific information, even if it has not passed through the lengthy rigors of FDA review procedures. Subpart II.C.1.b.ii. incorporates discussion of constitutional speech issues as they relate to the expedient distribution of scientific findings.

i. The Role of Practitioners in the Advancement of Treatments

Consider that engagement in research is rare in comparison to the practice of medicine. There are simply far fewer research laboratories than there are medical clinics and offices.[94] Moreover, the laboratories that do exist, if they are run according to sound scientific principles, employ meticulous and therefore time-consuming methodologies.[95] When scarcity of research facilities is combined with exacting and laborious methods, the development of findings will be slow.

In contrast, the larger corps of physicians who practice on a daily basis

93. Because the Modernization Act's liberalization of off-label marketing requires manufacturers to submit supplemental applications for off-label uses, the reforms that were adopted do not achieve the potential efficiencies that might have been obtained had no such requirement been included in the legislation. For discussion of the supplemental application requirement, see *infra* Subpart III.C.

94. The dynamics underlying this reality are as follows. Medical practitioners routinely set up individual and small-group practices that are financially feasible because of the direct support they receive through immediate collection of patient fees or imminent collection of insurance and Medicare reimbursement. Setting up research endeavors is more complicated and precarious, requiring establishment of expensive laboratories that are not funded by patient fees, but through government, corporate, or university funding. Because all of these sources of financing are scarce and subject to many conflicting claims, research laboratories will always be far fewer than medical care facilities.

95. *See* Braun v. Lorillard, Inc., 84 F.3d 230, 235 (7th Cir. 1996) (referring to "the scientist's creed of meticulous and objective inquiry").

may be compelled by economic forces to see many patients over the course of a year.[96] Although their contact with patients' problems and their treatment is far more informal than a scientist's contact, physicians nonetheless encounter many of the same challenges that researchers face. Through the processes of diagnosis, treatment, prescription, and post-treatment observation, doctors naturally will notice trends and develop theories of cause-and-effect that will be informally tested as their practices progress. Large numbers of doctors who share information through professional contact can exploit each others' informal findings, thereby becoming a likely source of some innovative drug applications.[97]

Physicians informally practicing as sole practitioners or in small groups have another advantage over formalized laboratory structures in the development of new theories—they are less likely to be subjected to bureaucratic constraints and institutional pressures in regard to their findings. To some extent or another, the formal research that occurs in laboratories is subjected to organizational forces.[98] Unfortunately, a dysfunctional relationship exists between innovation and centralized authority, which tends to constrain innovation.[99] Doctors typically have wide berth in interpreting observations. Despite the heralded objectivity of the scientific method,[100] scientists can be stifled and confined by the incentives and expectations established by the research institutions they serve.[101] As a result, the open-mindedness we expect from the scientific community might be more prevalent among observant medical

96. Indeed, many doctors see a large number of patients every day. *See* Andy Miller, *When You Grow Up to Be a Doctor*, ATL. J. & CONST., Apr. 4, 1994, at E3.

97. The developing liberalization of pharmaceutical law has included a recognition of the value of physicians' observations in advancing the state of medical knowledge. For example, the regulations that authorize physician-led parallel track treatment using experimental drugs require physician reporting of safety and efficacy information to drug sponsors. *See* 57 Fed. Reg. 13,258 (1992). This requirement suggests that regulators recognize the value of physicians' informal observations and learning during the course of treatment.

98. University labs that are typically funded through grants face pressure to mold both projects and findings in ways that increase the likelihood that grants will be extended, thereby ensuring the labs' continued survival. Private corporate labs are subject to the pressures of financial analyses that suggest certain facilities are superfluous or irrelevant to the corporate mission. Researchers working for pharmaceutical companies also may be directed in terms of the kind of research they are expected to do, and may be affected by knowledge of the kinds of results that would be considered most desirable and therefore be most highly rewarded.

99. *See* Steven R. Salbu, *Should AIDS Research Be Regulated? A Manhattan Project for AIDS and Other Policy Proposals*, 69 IND. L.J. 425, 440 (1994).

100. *See* Anne M. Coughlin, *Excusing Women*, 82 CAL. L. REV. 1, 73 (1994) (referring to "the 'scientific method[]' . . . , in which '[t]he objective data determine what is to be accepted as scientific truth'") (citation omitted).

101. Among other things, institutions can shape the research questions that get asked; the methodology ultimately adopted, including its particular flaws and biases; and the desirability of any one direction of findings over other directions of findings.

practitioners.

In this vein, a General Accounting Office report states that the FDA "could not review drugs in its lengthy testing process at a pace equal to that at which physicians discover beneficial off-label uses."[102] The result is that, while the FDA has tended to view labels as Bibles, medical practice frequently improves on approved indications and dosages, such that doctors who adhere strictly to labeled information are "behind the wave."[103]

ii. The Need to Expedite the Distribution of Sound Scientific Information, Even if It Has Not Passed Through the Lengthy Rigors of FDA Review Procedures

Despite the expense and scarcity of scientific laboratories in comparison to the more informal learning environments of medical practices, formal high-quality research is conducted today in many different settings. Pharmaceutical research is executed in private corporate laboratories, as well as at universities and not-for-profit research centers throughout the country and around the world.[104] Ordinarily, without government intervention, we would expect knowledge to be collected and shared by the scientific community, and to pass quickly to and throughout the medical community. FDA regulation of off-label promotion dampens this expectation.[105]

Off-label prescription relies on the expedient and unfettered diffusion of the wealth of information amassed in laboratories. Years before any FDA approval procedures could be navigated from start to finish, physicians read articles published by highly regarded scientists and medical researchers in peer-reviewed journals.[106] The optimally-informed

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102. GENERAL ACCOUNTING OFFICE, REPORT TO THE CHAIRMAN, COMM. ON LABOR AND HUMAN RESOURCES, U.S. SENATE, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES (1991).

103. William G. Castagnoli, *New Players Recast the PPI Debate*, MED. MKTG. & MEDIA, May 1996, at 44.

104. *See* Steven R. Salbu, *AIDS and Drug Pricing: In Search of a Policy*, 71 WASH. U. L.Q. 691, 722-24 (1993) (discussing various public and private forums in which government-sponsored pharmaceutical research is done).

105. *See Off-Label Info Okay: So What?*, IN VIVO, Dec. 1997, at 2 [hereinafter *So What?*] ("Industry and patient groups have long pointed out that [prohibiting off-label marketing] . . . prevents credible information from reaching physicians so they can treat patients according to the latest medical knowledge.").

106. While the peer-review process is imperfect, it also is a rigorous system under which research frequently undergoes several iterations of revision and resubmission. Although any review system that employs human assessors inevitably will have flaws, the use of scientists to evaluate blindly the work of their peers is probably the right conceptual start. For discussion of the peer review process and its strengths and weaknesses, see Lars Noah, *Sanctifying Scientific Peer Review:*

physician is introduced to the most current scientifically valid information[107] and incorporates it into his or her practice.[108] Arguably, the result is medical care that more closely approximates the scientific state of the art.[109]

A crucial factor in this process is the necessity of keeping doctors informed about the latest relevant research findings. Who is to accomplish this task? Manufacturers have the greatest incentive, as well as the resources, to spread the news of research findings that support new and beneficial off-label uses of their products. Liberalized off-label promotion therefore should yield the most progressive medical practice. As Polubinski notes, patients under such a system "may receive better, potentially life-saving treatments before the completion of the lengthy approval process."[110]

These and related arguments can be cast in terms of the value, and indeed the sanctity, of free speech, to be impeded only under compelling conditions.[111] Indeed, pharmaceutical manufacturers cast the issue of off-label marketing in terms of whether they should be denied the freedom to provide doctors with "truthful information."[112] The speech angle can be couched broadly in the context of the dialogue that exists among scientists, medical practitioners, and allied health professionals, and how crucial it is that "the flow of scientific information about off-label uses . . . not be unduly inhibited."[113] A reasonable argument can be made that, particularly

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Publication as a Proxy for Regulatory Decisionmaking, 59 U. PITT. L. REV. 677, 693-711 (1998).

107. *See Off-Label Use of Drugs an Issue: FDA and Pharmaceutical Research and Manufacturers of America Deal with Off-Label Drug Regulations*, CHAIN DRUG REV., Jan. 20, 1997, at RX6 (quoting PhRMA spokesperson Jeff Trewhitt, "Doctors should be allowed to have information about [off-label] . . . procedures as long as the information is valid and is documented scientifically.").

108. *See* Charles J. Walsh & Allisa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 913 n.123 (1996) ("With increasing frequency, physicians are prescribing off-label uses based on recent research or experiments, prior to the new use being approved by the FDA.").

109. Recall from the preceding Subpart that a large army of doctors can make valuable medical discoveries in the course of their own practices. This process is furthered when doctors are given open access to credible scientific and medical knowledge as soon as it is published, without need to wait for bureaucratic approval. Doctors can use this information to develop the logical, scientifically supported, creative off-label treatments that arise in the course of medical practice.

110. Polubinski, *supra* note 33, at 1005.

111. *See FDA Charged with Rights Violation*, BUS. & HEALTH, Feb. 1996, at 9 (noting concerns of civil libertarians that off-label advertising restrictions violate the speech rights of both providers and recipients).

112. Jill Wechsler, *Back to the Future? The Rise and Fall of Reform*, PHARM. EXEC., Dec. 1996, at 58 (noting, prior to the passage of the Modernization Act, that "[a] key goal for pharmaceutical marketers was to gain more leeway in providing doctors with 'truthful information'").

113. Charles J. Walsh & Alissa Pyrich, *FDA Efforts to Control the Flow of Information at*

in regard to advertisements aimed at professionals, the marketplace of conflicting ideas is the most appropriate protection against incomplete, inaccurate, or otherwise misleading data.[114] This approach "comports with the Supreme Court's preference for combating potentially problematic speech with more speech."[115]

Richard A. Samp, Chief Counsel of the Washington Legal Foundation, notes that, "in its zeal to protect the American public, the FDA apparently has overlooked the very real First Amendment concerns created by its policies."[116] He further charges that "[b]y attempting to suppress truthful information about FDA-approved drugs and devices, the agency appears to be infringing on the constitutional rights of speakers to convey such information and of listeners (most of them medical professionals) to receive such information."[117] The result is that doctors and other health care practitioners and professionals may be suboptimally, or even inadequately, informed.[118]

Finally, any approach more restrictive than broadly permissible off-label marketing can thwart vigorous discussion and debate. The result could be to retard the development of optimal patient treatment regimes. U.S. District Court Judge Royce C. Lamberth recently supported this perspective, ruling in July of 1998 that off-label promotions constitute protected commercial speech that cannot be unduly restricted by government regulation.[119]

These potential social benefits of off-label practices are indeed compelling, but as noted in the following Subpart, they are eroded to some degree by a number of costs, particularly risks to the public that are

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Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose, 24 SETON HALL L. REV. 1325, 1354 n.158 (1994) (referring to comments in speech by Michael R. Taylor) (citation omitted).

114. Reliance on the marketplace of ideas for consumer protection appears stronger in cases like this than it may appear in other cases. I refer here to the fact that the marketplace of ideas upon which we would rely in this instance would be used by health care practitioners and other professionals. Logically, we can expect the marketplace of ideas to protect against the effects of bad information most effectively among well-educated participants who have access to many information sources. The practitioners and professionals at issue are likely to fall in this category.

115. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 73 (D.D.C. 1998).

116. Richard A. Samp, *FDA Faces Court-Ordered Limits to Its Powers*, MED. MKTG. & MEDIA, Sept. 1997, at 50.

117. *Id.*

118. *See* Michael F. Conlan, *Not Good Enough: Some Feel FDA's Easing of Off-Label Rules Still Falls Short*, DRUG TOPICS, Jan. 22, 1996, at 68 (discussing contention of Jeff Trewitt that pre-Modernization Act FDA off-label marketing reforms were inadequate to keep health care practitioners sufficiently well-informed).

119. *See Washington Legal Found.*, 13 F. Supp. 2d at 74. For discussion, see Rochelle Sharp, *Some Restrictions on Drug Makers' Ability to Promote Off-Label Uses Are Overruled*, WALL ST. J., July 31, 1998, at A12.

associated with untested and unapproved applications.[120] To make their strongest arguments in favor of off-label applications, proponents need to address this potentially substantial downside. One possible way to do this is through the age-old compromise of substituting paternalistic protection with information.[121] If the potential benefits of off-label use outweigh the potential costs, and the public risks are clearly disclosed, one can argue that reduced regulation increases social utility. While disclosure efforts of the past have tended to focus on manufacturer disclosures,[122] which directly reach physicians rather than the public, disclosure in this instance would likely include statements by doctors to patients warning them that off-label applications have not been subjected to FDA scrutiny.[123]

2. Arguments Disfavoring Off-Label Processes

Opponents of off-label processes converge, albeit from a variety of starting points, upon a single basic objection—that the lack of regulatory control over off-label applications endangers human health and human life. Subpart II.C.2.a. explains this basic premise and provides an example of the potential pitfalls of liberal off-label policies; the Subparts after that concern some of the particular problems that critics associate with the absence of FDA oversight. Subpart II.C.2.b. examines the contention that off-label applications are the equivalent of experimental treatments and should be treated as such. Subpart II.C.2.c. looks at an argument that has been lodged specifically at legalized off-label marketing—the contention that permitting off-label promotions of drugs will discourage manufacturers from investigating the effectiveness and safety of off-label uses. Subpart II.C.2.d. describes the pressures and conflicts of interest that can contaminate the content of off-label promotions. Subpart II.C.2.e. discusses responses to the free speech arguments of off-label marketing proponents.

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120. *See infra* notes 124-48 and accompanying text.

121. *See* John M. Blim, Comment, *Free Speech and Health Claims Under the Nutrition Labeling and Education Act of 1990: Applying a Rehabilitated* Central Hudson *Test for Commercial Speech*, 88 NW. U. L. REV. 733, 755 (1994) (noting argument that access to all information and freedom of individuals to make their own judgment using that information are superior to paternalistic protections).

122. *See, e.g.*, Richard Haugh, *Label Fable?*, HOSPITAL & HEALTH NETWORKS, Feb. 20, 1998, at 82 (discussing bill to require medical device manufacturers "to include a warning that off-label uses weren't necessarily safe or effective and could even be harmful").

123. Presently, physicians are not required by law to inform patients that a treatment they are receiving involves an off-label use of a drug. *See supra* notes 57-58 and accompanying text.

a. The General Argument that Lack of Regulatory Control Over Off-Label Applications Endangers Human Health and Human Life

Let's admit for the moment that supporters are correct in asserting that off-label practices expedite the discovery and the diffusion of some effective patient treatments. Critics would remind us that these benefits come at a price. Even if off-label uses are as prevalent in today's practice of medicine as proponents suggest, such entrenchment could be a bad thing as easily as a good thing.[124] This would be true, for example, if many of the common off-label uses were to prove ineffectual, harmful, or both.

Is this scenario plausible? Napoli notes that while some off-label drug uses are relatively harmless, others are "costly, threatening, and highly toxic."[125] This should not be surprising, given that both the off-label prescription and the off-label use of a drug lack the FDA imprimatur, and therefore also lack the consumer safeguarding we usually associate with prescription drugs.[126] The law requires that manufacturers submit rigorously developed evidence of safety and efficacy to receive approval to market a drug for purposes noted in the labeling.[127] No such requirement is imposed in regard to subsequent, off-label uses. Accordingly, information regarding proper dosage, as well as drug safety and efficacy for the off-label application, need not be collected or recorded.[128] These dynamics have led to concerns "that physicians and consumers will be misled into relying on scientific logic or scanty data supporting a particular use, without adequate well-controlled clinical trials that prove definitively that the drug works."[129]

Consider an example.[130] Public Citizen has highlighted the fen-phen experience as "a textbook study of why . . . off-label promotions . . . are so

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124. *See* Sean Turner et al., *Unlicensed and Off Label Drug Use in Paediatric Wards: Prospective Study*, BRIT. MED. J. 343, 344 (1998) (stating that while off-label uses of drugs to treat children are widespread, it is unclear whether such uses are appropriate).

125. *Chemotherapy and Informed Consent*, HEALTHFACTS, Sept. 1997, at 1, 5.

126. For this reason, before the FDA was required under the Modernization Act to allow certain off-label promotion practices, it insisted that off-label marketing would "undermine the integrity of the entire drug approval process." *Zeroing in on Advertising and Promotion*, PHARM. EXEC., Nov. 1996, at 20.

127. *See* 21 C.F.R. § 312 (1998).

128. *See* Nancy A. Wynstra, *Breast Cancer: Selected Legal Issues*, 74 CANCER 491, 505 (1994).

129. Nancy K. Plant, *Prescription Drug Promotion on the Internet: Tool for the Inquisitive or Trap for the Unwary?*, 42 ST. LOUIS U. L.J. 89, 129 (1998).

130. While the forthcoming example has been the most salient one put forth in very recent years, earlier criticism of off-label practices has focused on other drugs and products, such as Retin-A, silicone, and collagen injections. *See* Michael Unger, *More Bite Urged for Watchdog FDA*, NEWSDAY, Nov. 24, 1992, at 29.

dangerous."[131] The group notes that the FDA-approved drug fenfluramine, the "fen" portion of fen-phen, was "widely used off-label in three ways"[132] prior to the FDA's determination that the drug presented "an unacceptable risk."[133] These common off-label uses included use in combination with phentermine (the "phen" portion of fen-phen), the extended use of fenfluramine beyond the brief approved periods, and the use of fenfluramine by persons overweight but not obese.[134] Public Citizen further cites the FDA's conservative estimate that 285,000 fen-phen users suffered damage to heart valves during the brief period in which the combination was widely prescribed.[135] It suggests that this tragedy resulted from an eighty-fold increase in fenfluramine prescriptions following the release of a 1992 study, which confirmed long-term weight-loss efficacy via the off-label combination of fenfluramine with phentermine.[136] Indeed, by 1996, doctors wrote 18 million prescriptions for these two drugs.[137]

This enormous increase in fenfluramine prescriptions predated the legalization of off-label marketing.[138] In other words, doctors began prescribing fenfluramine in tandem with phentermine not because manufacturers pressured them with an advertising blitz, but simply because the doctors read the primary scientific evidence, or read about the scientific evidence in secondary sources, or heard about the scientific evidence by word of mouth.

This suggests two possible conclusions: (1) the legalization of off-label prescription and use is enough, in itself and without the legalization of off-label marketing, to promote devastating injury to the public health; and (2) legalized off-label marketing logically would have exacerbated the damage. Had the manufacturer of fenfluramine been permitted to market the drug in off-label combination with phentermine and to a wide array of patients, many more people might have used and been injured by the drug.[139]

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131. Public Citizen, *Fen-Phen Fact Sheet*, (visited Feb. 3, 1998) <http://www.citizen.org/public_citizen/congress/fda/S.%20830-FDA/fenfacts.htm> [hereinafter *Fact Sheet*].

132. *Id.*

133. *FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine*, HHS NEWS, Sept. 15, 1997, at 97-32.

134. *See Fact Sheet*, *supra* note 131.

135. *See id.*

136. *See id.*

137. *See* Ronald M. Schwartz, *FDA Warning on Rx Diet Combo*, AM. DRUGGIST, Aug. 1997, at 22.

138. The 1992 study preceded by five years the Modernization Act, which in 1997 legalized qualified off-label marketing of prescription drugs. *See infra* Part III.

139. An alternative and obverse argument can be made here, however. Perhaps the history of fen-phen and the proliferation of fenfluramine prescriptions in its wake highlight the pervasiveness

b. The Contention that Off-Label Applications Are the Equivalent of Experimental Treatments and Should Be Treated as Such

Critics have argued that legalized off-label applications subject the public to treatment with what are closely analogous to, or even identical to, experimental drugs. The vernacular of "experimenting on the public" thus has made its way into the off-label debate. For example, a spokesperson for Public Citizen suggests that off-label marketing permits drug consumers to "become part of an uncontrolled experiment where no one is keeping track of . . . who's helped and who's hurt."[140] This critical perspective has been echoed by a highly regarded medical school faculty member.[141] Likewise, some insurers[142] and HMOs[143] classify off-label use as experimental and therefore non-reimbursable.

The experimental drug analogy is predicated on a characteristic shared by new drugs that have never undergone FDA review and off-label uses of FDA approved drugs—in each instance, the use at issue has never undergone scrutiny by the agency. Recall that a basic function of the FDA is the protection of patients from dangerous drugs.[144] From the perspective of patients' safety concerns, off-label use of approved drugs is arguably indistinguishable from use of entirely unapproved drugs. Given that neither one has passed regulatory muster, how can the two be differentiated? Permitting unapproved uses and prescriptions, not to mention their marketing, may be inconsistent with the regulatory structure that governs

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of information and its accessibility to doctors in an information era, regardless of and apart from any manufacturer marketing efforts. Under this theory, off-label promotion by the manufacturer would not have exacerbated this fiasco, because virtually all doctors would have read about off-label use in the original articles or in news articles covering the findings, or else would have heard of the off-label use through informal conversations with associates.

140. *FDA to Ease "Off-Label" Use Restrictions*, HEALTH LINE, June 8, 1998, *available in* LEXIS, News Library, Allnws File.

141. *See* Deborah Gesensway, *Coming Soon: Off Label Marketing; Changes at FDA Mean Faster New Drug Approvals—and More Promotion*, AM. C. OF PHYSICIANS OBSERVER ONLINE, (visited July 26, 1998) <http://www.acponlin.org/journals/news/dec97/offlabel.htm> (quoting Paul D. Stolley, University of Maryland School of Medicine chair of epidemiology and preventive medicine, "[T]his is a very uncontrolled part of medical practice. Doctors are doing uncontrolled experimentation in their own practices, and the American people are being experimented on because the drugs aren't being tested adequately.").

142. *See* Melody L. Harness, Note, *What is "Experimental" Medical Treatment?: A Legislative Definition Is Needed*, 44 CLEV. ST. L. REV. 67, 72 (1996).

143. *See* Kent G. Rutter, Note, *Democratizing HMO Regulation to Enforce the "Rule of Rescue,"* 30 U. MICH. J.L. REFORM 147, 185 (1996).

144. *See* Myron L. Marlin, Comment, *Treatment INDs: A Faster Route to Drug Approval?*, 39 AM. U. L. REV. 171, 189 n.172 (1989) ("[D]etermination of actual safety and effectiveness of particular drugs is one of [the] essential functions of FDA. . . ." (citing Lemmon Pharmacal Co. v. Richardson, 319 F. Supp. 375, 377 (E.D. Pa. 1970))).

pharmaceutical access.

Wilsker has taken this critical perspective regarding off-label practices to its logical conclusion, suggesting that an off-label combination of two FDA-approved drugs should be treated as a new drug[145] subject to the FDA's ordinary new drug application processes.[146] He observes that two drugs that are harmless taken individually can become deadly in combination.[147] If the safety of the individual drugs may have no bearing on the safety of the combination, the FDA can carry out its mission—the monitoring of pharmaceuticals to provide reasonable assurance of public safety—only by examining the combination as a separate and distinct entity, with every bit as much rigor as it would apply to an ordinary new drug application.[148]

c. The Contention that Permitting Off-Label Promotions of Drugs Will Discourage Manufacturers from Investigating the Effectiveness and Safety of Off-Label Uses

The preceding Subparts have addressed criticism lodged very broadly against all off-label practices, including off-label use, prescription, and marketing of drugs. Yet despite these concerns, off-label use and prescription of FDA-approved drugs are widespread practices accepted today.[149]

Off-label marketing and promotion have been more controversial.[150] Prior to the passing of the Modernization Act, the FDA consistently rejected the off-label marketing of drugs under the theory that it would eliminate company incentives to engage in post-approval research regarding new, unlabeled applications.[151] If a manufacturer can market its drugs for any and all uses once the drugs have been approved for one treatment, why should it spend time and money to study the safety and effectiveness of off-label applications?[152] The FDA was concerned that

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145. *See* Jaime A. Wilsker, Note and Comment, *One-Half Phen in the Morning/One Fen Before Dinner: A Proposal for FDA Regulation of Off-Label Uses of Drugs*, 6 J.L. & POL'Y 795, 844 (1998).

146. *See id.* at 846.

147. *See id.* at 845.

148. *See id.* at 848-49.

149. *See supra* notes 70-79 and accompanying text.

150. *See* Alicia Ault, *Further Controversial Provision in the Bill*, 350 LANCET 1690 (1997) (referring to off-label promotion as one of "the most controversial elements" of the reform bill leading to the Modernization Act).

151. *See* Alicia Ault Barnett, *FDA Proposes Easing of Promotion Rules*, 347 LANCET 52 (1996); Wayne L. Pines, *New Challenges for Medical Product Promotion and Its Regulation*, 52 FOOD & DRUG L.J. 61, 64 (1997).

152. One possible answer is that, before the Modernization Act, manufacturers would study safety and effectiveness of off-label uses in order to manage product liability risks. Under this

manufacturers would get approval for a "cheap, narrow indication and the next day begin selling the drug for multiple, broad, and profitable other indications."[153] In short, off-label marketing seemed to enable drug makers to circumvent existing regulatory protections.

d. Identification of Pressures and Conflicts of Interest that Can Contaminate the Content of Off-Label Promotions

The problems identified so far may be exacerbated by widespread conflicts of interest; indeed, three important groups—manufacturers, physicians, and scientists—all face either conflicts of interest or incentives that encourage potentially risky off-label practices. The potential conflicts of each group are discussed in the Subparts below.

i. Manufacturers' Conflicts

The pressures placed on pharmaceutical companies through the profit motive is an implicit factor behind regulation of the pharmaceutical industry. If drug companies were in the business of protecting the public from potentially harmful products, they could and would spend their vast resources hiring personnel to achieve this end, perhaps more effectively than the FDA does. Drug companies, however, are in the business of selling pharmaceutical products for a profit, and the pressures to do this effectively can tempt companies to take imprudent risks with public health.

Of course, potential liability certainly should act at least to discourage the precipitate introduction of unproven drugs and marketing of off-label uses. Nonetheless, the need to meet quarterly earnings expectations can be a powerful incentive to introduce promising new products prematurely.[154] The imposition of the FDA between the manufacturer and the market is intended in large part to protect the public against this kind of dynamic. If companies would be tempted to release dangerous products prematurely without the existence of the FDA-approval buffer, why would they not be tempted to market dangerous off-label uses if permitted to do so freely?

Moreover, the temptation to engage in inadvisable marketing practices is not limited to struggling companies lacking successful products.

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theory, a manufacturer would be foolish, and indeed potentially negligent, to market off-label uses without data supporting the safety and effectiveness of those uses. In any event, the legislation that authorized off-label marketing in 1997 resolved this issue by requiring manufacturers, subject to certain possible exemptions, to submit supplemental applications in order to disseminate off-label information. *See* 21 U.S.C. § 360aaa-3 (1997).

153. James G. Dickinson, *FDA Letter, Deputy's Speech, Define a Dilemma*, MED. MKTG. MEDIA, Oct. 1996, at 12.

154. *See, e.g., Drug Firm to Plead Guilty to Lying to FDA Officials*, ORLANDO SENTINEL, Feb. 28, 1991, at A17 (reporting pharmaceutical company admission that it sold adulterated, mislabeled medicine).

Koberstein observes that pharmaceutical companies face pressure to support potentially harmful off-label uses of highly profitable drugs.[155] He notes that soaring sales heighten potential conflicts because "[b]lockbusters rule the world of pharmaceuticals, and no company wishes to risk the fortunes of a star."[156] If pressures on successful companies encourage either support for or at least tolerance of risky off-label practices, imagine the effect of pressures on companies that are performing precariously.

ii. Doctors' Conflicts

Doctors likewise face a number of potential conflicts of interest that may encourage the imprudent prescription of drugs for off-label use. Some pharmaceutical companies, despite the objections of ethicists and other critics,[157] continue to confer gratuities of varying value on physicians[158] who, as a group, are the legally required intermediaries necessary for the prescription of the companies' products.[159] Doctors who accept tokens from drug manufacturers place themselves in potential positions of either blatant or subtle indebtedness, a process capable of clouding judgment in the treatment of patients.[160]

Doctors face a second variety of pressure from patients, who come to them not only with conditions, but also with pre-established ideas of the medications they expect to receive.[161] While this source of pressure on

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155. *See* Wayne Koberstein, *Living Off-Label*, PHARM. EXEC., May 1997, at 12.

156. *Id.*

157. *See Advertising, Marketing and Promotional Practices of the Pharmaceutical Industry: Hearings Before the Senate Comm. on Labor and Human Resources*, 101st Cong., 2d Sess. at 159 (1990) (testimony of AMA House of Delegates Vice Speaker Dr. Daniel H. Johnson, questioning "undue influence from a gift . . . with strings attached").

158. *See* Susan Heilbronner Fisher, Note, *The Economic Wisdom of Regulating Pharmaceutical "Freebies,"* 1991 DUKE L.J. 206, 210, 211-12 (noting that pharmaceutical company "retailers" often treat physicians to meals and "freebies," and pharmaceutical companies pay physicians substantial honoraria to speak at company-sponsored conferences and mention the sponsor's product); John C. Nelson, *A Snorkel, a 5-Iron, and a Pen*, 264 JAMA 742 (1990) (noting conferral by drug companies of free resort vacations to physicians and spouses).

159. *See* Richard L. Cupp, Jr., *Rethinking Conscious Design Liability for Prescription Drugs: The Restatement (Third) Standard Versus a Negligence Approach*, 63 GEO. WASH. L. REV. 76, 84 (1994) (noting physician prescription requirement for many drugs and medical devices).

160. *See* David Orentlicher, *The Influence of a Professional Organization on Physician Behavior*, 57 ALB. L. REV. 583, 593 (1994) (noting increased tendency in recent years for pharmaceutical companies to provide gifts that are "particularly likely to influence the treatment decisions of physicians").

161. *See, e.g.*, Cheryl Clark, *Drug Commercials: A Prescription for Trouble?*, SAN DIEGO UNION-TRIB., July 20, 1998, at A1 (describing patient who said to doctor, "The ad said I should be on Pravachol. How come you didn't put me on that?").

As one commentator notes, when a pharmaceutical product becomes a resounding success,

doctors has always existed, and of course is at some level unavoidable, it is also heightened today by several factors. The FDA recently loosened its restrictions on manufacturers' direct advertising of prescription drugs to consumers.[162] As a result, today's patients are bombarded by the efforts of pharmaceutical manufacturers to spur user demand.[163] Commercials that end with the phrase, "If you have condition X, see your doctor about treatment Y," can be expected to exacerbate the pressures patients place on physicians.[164]

Combine this phenomenon with the more generic overall growth and increasing public accessibility of a wealth of information through the development of various media. As cable and satellite channels, periodicals, and Internet sites grow in number and as more subscribers gain access to their abundant information,[165] more patients are likely to arrive at their doctors' offices with preconceived ideas of the treatments they expect. The result over time is an increasingly empowered population of patients. Of course, this trend will have some positive side effects, such as protecting patient rights and enabling patients to be more informed participants in their own treatment. On the other side, however, is the inevitability that better-informed, empowered patients will become more demanding, placing greater pressures on doctors to prescribe particular drug treatments. As they face larger numbers of imperious patients whose patronage provides their livelihood, doctors will have to be very strong to resist pressures to prescribe requested off-label treatments.[166]

"[s]tar-struck customers rush in like moths to a flame." Koberstein, *supra* note 155, at 12.

162. *See* 62 Fed. Reg. 21,684 and 21,685 (1997).

163. *See* Michael Lasalandra, *Advertised Drugs Find Patient Following*, BOSTON HERALD, Mar. 15, 1998, at 21 (noting heavy television and general circulation magazine advertising of certain prescription drugs).

164. As examined in Part III discussing the precise limits of the Modernization Act, drug manufacturers are permitted to promote off-label uses only to a specified group of practitioners and other professionals, and not directly to patients. *See infra* note 185. This fact, while certainly relevant to the discussion here, does not remove the concerns that pressures placed on physicians by patients are growing. Even though pharmaceutical companies cannot market off-label uses directly to consumers, they can market labeled uses, and the off-label alterations will frequently treat the same disease, condition, or symptoms. Moreover, while the manufacturers cannot tout the off-label variants, others can and do, over web pages on the Internet, or through word of mouth. As direct-to-consumer advertising of closely related labeled uses are combined with an increasingly open marketplace for the exchange of information, many consumers can and will learn a lot about off-label applications and place demands for such applications on their health care providers.

165. *See* Michael H. Cohen, *Holistic Health Care: Including Alternative and Complementary Medicine in Insurance and Regulatory Schemes*, 38 ARIZ. L. REV. 83, 140 n.416 (1996) (noting information access via technology is transforming peoples' response to disease, particularly in terms of increased autonomy).

166. An example of this phenomenon is the off-label prescription of fentermine in combination with the prescription drug phenfluramine, as part of the widely touted blockbuster that was commonly called "fen-phen" during the middle 1990s. As word of mouth spread regarding the

iii. Scientists' Conflicts

Even scientists, presumably insulated from such conflicts of interests, lack complete objectivity. One obvious problem is promotion of off-label uses by scientists with undisclosed financial ties to manufacturers.[167] Such scientists have the same monetary conflict of interests as the manufacturers with whom they are associated.

Even scientists with no hidden investments or direct stakes in a manufacturing company may encourage off-label drug uses that tend to highlight the importance of their research. Altman observes, "scientists, proud of their research that showed a new therapy worked, often encourage off-label use to enhance their reputations."[168] As in the case of both manufacturers and physicians, scientists are in a position that raises a conflict of interest.

Of course, we cannot ignore the powerful professional ethos that encourages scientists to be objective and rigorous in the application of unbiased methodologies.[169] Yet we likewise cannot ignore the demands of a highly competitive profession in which researchers strive to become stars.[170] Scientists too frequently are charged with fraud in the execution of their experiments.[171] In this setting, competitive pressures that lure

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effectiveness of this treatment, patients went to physicians in large numbers asking for fen-phen. In all likelihood, many or most of the patients looking for fen-phen were unaware that the treatment was an off-label combination that had never received the FDA's sanction. Moreover, the patients who went to their doctors in droves requesting this particular treatment placed pressure on those practitioners to prescribe a very popular but nonetheless controversial drug combination, about which many of the doctors had reason to be concerned. Logic tells us that some of these doctors were affected by patient pressure and demands in exercising their best judgment. In the wake of the removal of fenfluramine from the market in 1997, the hazards of conflicts of interest facing physicians is apparent. For more detailed discussion of this example, see *supra* notes 130-39 and accompanying text.

167. *See* Donald M. Payne, *Consumers at Risk: Off-Label Uses of Medical Drugs and Devices*, TRIAL, Aug. 1993, at 26 (reporting "improper promotion" of acne treatment for off-label uses by scientists who had hidden financial ties to the manufacturer).

168. Lawrence K. Altman, *Good News from the Front in the War Against Cancer*, N.Y. TIMES, May 26, 1998, at F3.

169. Ethical mandates exist in both business and the practice of medicine. As these mandates do not remove conflict of interest problems in these contexts, so they cannot eliminate conflict of interest problems even in the highly structured world of scientific research. While we hope and believe that the existence of ethical precepts will reduce the incidence of self-serving behaviors that are likely to harm others, we would be naïve to believe that the principles of any profession always serve this function.

170. For discussion of the extremely competitive nature of scientific research, see Salbu, *supra* note 99, at 445-46.

171. *See, e.g.*, Imre Karacs, *Love in the Lab of the Gods*, INDEPENDENT (LONDON), July 2, 1997, at 2 (discussing charges against an eminent scientist of "systematic forgery," "faking

professionals from absolute purity and objectivity are an inescapable reality.[172] Scientists face incentives not only to encourage off-label applications consistent with their own findings, but also to skew either data analysis or data interpretation in the direction of promising new treatments, the proliferation of which might raise their stature in the scientific and medical communities.[173]

e. Responses to the Free Speech Arguments of Off-Label Marketing Proponents

Opponents of off-label advertising and promotion can challenge the free speech arguments of proponents by asserting that commercial speech rights are limited, that the entirely uncontrolled flow of ideas in the medical and allied health communities can be socially harmful in certain limited instances, and that existing restrictions are limited and therefore reasonable.[174] Specifically, they can contend that companies are not precluded under the Modernization Act from advertising off-label uses; they simply must comply with the statute's safeguards to do so.[175]

Whereas open discussion of high-quality, reliable research findings can foster medical advances, the same may not hold true as the quality deteriorates. At the extreme, the dissemination of unreliable data or irresponsibly conducted research could lead to potentially deadly medical practices. Free speech proponents likely will reply that quackery is best countered by challenge and debate rather than by stifling the flow of information.[176] Still, limited quality control over marketing practices of manufacturers, in the interest of consumer protection, is not the same as absolute censorship over noncommercial exchanges of ideas. The dangers of the former restriction arguably are less formidable than the dangers of the latter, and the protection in question could preserve human safety in an environment characterized by complex information that is difficult to evaluate under the best of circumstances.

Public Citizen has issued statements over the Internet that challenge both the motives and the effects of the reform, highlighting the commercial nature of the speech in question. In one such release, the highly regarded academic Dr. Arnold S. Relman contends that drug manufacturers have

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experiments," and "defrauding public institutions to the tune of possibly millions of marks").

172. *See* Philip M. Boffey, *Rise in Science Fraud is Seen; Need to Win Cited as a Cause*, N.Y. TIMES, May 30, 1985, at B5 (noting agreement of medical professionals and journal editors that fierce competition in science provokes fraud and deception, undermining the integrity of scientific research).

173. *See* Altman, *supra* note 168.

174. *See supra* notes 111-19 and accompanying text.

175. For discussion of these safeguards, see *infra* Part IV.

176. For more discussion of the "marketplace of ideas" approach, see *infra* Part IV.

pressed for the change in law simply in order to make even more money than they have made in the past.[177] He observes that doctors "don't need their mailbox[es] full of high-powered marketing materials from drug companies urging them to use a drug for uses that have not been approved."[178] According to Dr. Relman, either credible evidence of the safety and effectiveness for such unapproved uses of the drugs is lacking, or else the manufacturers simply have not bothered to present existing data to the FDA.[179] Under either condition, the public might reasonably be skeptical about such uses of prescription drugs. Indeed, FDA panels have periodically assessed common off-label uses and found them to be ineffective or dangerous, culminating in a recommendation that the drug's labeling be revised to include warnings against the off-label use at issue.[180]

How high, then, is the social cost of requiring FDA safety and effectiveness approval prior to the promotion of off-label uses? Critics see the risks of off-label marketing as substantial, and the imposition on speech rights as constrained and reasonable. Inherent in their arguments is the notion that limited regulation of commercial speech is more than justified by the anticipated savings in health and lives.

III. THE FOOD AND DRUG MODERNIZATION ACT OF 1997: PROVISIONS RELATING TO OFF-LABEL PROMOTION AND MARKETING OF DRUGS

For the first time in recent years, drug manufacturers are permitted by statute to engage in the off-label marketing and promotion of the drugs they produce, subject to a variety of legislative constraints.[181] The authority to do so was established in the Modernization Act,[182] passed by Congress

177. *See* Public Citizen, *Statement of Dr. Arnold S. Relman, Editor-in-Chief Emeritus, New England Journal of Medicine; Professor Emeritus, Harvard Medical School, on S.830, The Senate FDA Bill*, Sept. 23, 1997, (visited Feb. 3, 1998) <http://www.citizen.org/public_citizen/congress/fda/S.%20830-FDA/relman.htm>.

178. *Id.*

179. *See id.*

180. *See, e.g.*, Michael F. Conlan, *One Calcium-Channel Blocker Form Flagged By FDA Advisors*, DRUG TOPICS, Feb. 19, 1996, at 48 (noting FDA advisory panel's recommendation that labeling of shortacting or immediate-release nifedipine be revised to warn physicians against off-label use for particular conditions).

181. Because proponents of the freedom to engage in off-label marketing view the legislative constraints as severe impediments, they continue to challenge the existence of any and all regulatory and legislative rules in court. A recent district court decision has supported their position. *See* Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998). If future district courts and appellate courts concur, it is possible that some or all of the statutory constraints that presently encumber absolutely free off-label marketing could be judicially lifted.

182. Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 301 (1997).

in 1997 amidst political maneuvering and bargaining,[183] much of which was a roller-coaster ride for the off-label advertising provisions.[184] The Subparts below include an introduction to the basic changes contained in these provisions of the legislation, and a discussion of the various provisions and contingencies that constrain the absolute freedom of manufacturers in the marketing of off-label applications.

A. *An Introduction to the Basic Changes Contained in the Modernization Act's Off-Label Marketing Provisions*

The Modernization Act permits manufacturers to disseminate to a number of groups, including (1) health care practitioners, (2) pharmacy benefit managers, (3) health insurance issuers, (4) group health plans, and (5) federal or state governmental agencies, qualified forms of "written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device. . . ."[185] To qualify under this provision, a manufacturer of a drug must either have filed an application or have received a biologics license for the drug under appropriate provisions of the Public Health Service Act.[186]

This generic description of the legislative provisions seems to suggest that companies are allowed to engage freely in the marketing of off-label applications. Critics of the reform say this is not the case. They contend that the legislation's detailed requirements are prohibitive.[187] The Subparts below cover the major constraining provisions of the legislation—ancillary requirements that arguably stifle the technically permissible off-label marketing of drugs.[188] They include an "authorized information" restriction, the supplemental application requirement, disclosure requirements, and a provision allowing for corrective actions.

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183. For discussion of this process in regard to the Modernization Act, see James G. Dickinson, *Winning on the Washington Yo-Yo*, MED. MKTG. & MEDIA, Sept. 1997, at 10.

184. *See* James G. Dickinson, *Marketers Miss Out Again on Capitol Hill*, MED. MKTG. & MEDIA, July 1997, at 10.

185. 21 U.S.C. § 360aaa(a) (1997).

186. *See id.* § 360aaa(b)(1)(A).

187. *See* Jack Angel, *Highlights (and Pitfalls) of the FDA Reform Bill*, MED. MKTG. & MEDIA, Jan. 1998, at 48 (noting concern, in regard to the Modernization Act's off-label provisions, "whether anyone would ever run this gauntlet. . . .").

188. Although critics contend the constraining provisions have this stifling effect, consumer safety advocates and the FDA can counter that the restrictions are required to protect the public from poor quality research, and biased or contaminated data.

B. *The Authorized Information Restriction*

Qualified manufacturers are permitted to provide to the enumerated groups[189] only "authorized information"[190] in the form of unabridged peer-reviewed articles[191] or qualified reference publications.[192] Among the more controversial limitations[193] is a provision that restricts qualified peer-

189. *See* 21 U.S.C. § 360aaa(a) (1997).

190. *Id.* § 360aaa-1(a).

191. *See id.* § 360aaa-1(a)(1)(A). Specifically, the statute defines this as

> an unabridged . . . reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts. . . .

Id. The statute defines a "scientific or medical journal" as

> a scientific or medical publication . . . that is published by an organization . . . that has an editorial board; . . . that utilizes experts, who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles; and . . . that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors or contributors involved with the journal or organization; . . . whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization; . . . that is generally recognized to be of national scope and reputation; . . . that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and . . . that is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

Id. § 360aaa-5(5).

192. *See id.* at 360aaa-1(b). The statute defines a "reference publication" as

> a publication that . . . has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer of a drug or device; . . . has not been edited or significantly influenced by such a manufacturer; . . . is not solely distributed through such a manufacturer but is generally available in bookstores or other distribution channels where medical textbooks are sold; . . . does not focus on any particular drug or device of a manufacturer that disseminates information under section 360aaa and does not have a primary focus on new uses of drugs or devices that are marketed or under investigation by a manufacturer supporting the dissemination of information; and . . . presents materials that are not false or misleading.

Id.

193. Groups such as the Coalition of Health Care Communicators believe that the limitation is overly restrictive. In 1996, they proposed to the FDA that off-label marketing be permitted

review articles to those "indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health,"[194] a requirement that restricts qualified information to an arguably elite group of publications.[195] To be disseminated, the information cannot have been "derived from research conducted by another manufacturer," unless "the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination."[196]

Sixty days prior to disseminating the information, the manufacturer must furnish the Secretary of Health and Human Services (Secretary) a copy of the information it plans to distribute, as well as clinical trial information the manufacturer has regarding the off-label use's safety and effectiveness.[197] The manufacturer also must forward to the Secretary any reports it has concerning the safety and effectiveness of the off-label use.[198]

C. *The Supplemental Application Requirement*

The legislation addresses one of the critics' concerns that we observed earlier[199]—the fear that off-label marketing could endanger the public by discouraging research on new uses of approved products. Specifically, critics have suggested that permitting manufacturers to engage in off-label marketing logically reduces or eliminates their incentive to study the safety and effectiveness of off-label uses.[200]

Although free-market adherents might contend that this problem is illusory,[201] the statute nevertheless addresses the concern by requiring the

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provided the materials distributed were prepared independently of the manufacturer, were peer-reviewed, were not selectively abridged or edited to skew the information in the manufacturer's favor, were prominently identified as concerning off-label uses, and were accompanied by a recommendation to consult FDA product information prior to prescription. *See Off-Label Drug Info Dissemination Comes Under Increasing Pressure*, MED. MKTG. & MEDIA, Mar. 1996, at 6.

194. 21 U.S.C. § 360aaa-5(b) (1997).

195. *See* James G. Dickinson, *Tiny Concession Splits Industry*, MED. MKTG. & MEDIA, Nov. 1997, at 12 (noting statutory restriction and its omission to include the output of many smaller publishers).

196. 21 U.S.C. § 360aaa(b)(3) (1997).

197. *See id.* § 360aaa(b)(4).

198. *See id.*

199. *See supra* Section II(c)(2)(c).

200. *See U.S. FDA on Dissemination of Off-Label Use Info*, MARKETLETTER, June 15, 1998, *available in* LEXIS, News Library, Allnws File (noting concerns that permitting manufacturers to disseminate information about off-label applications would reduce their incentives to create efficacy and safety data concerning the off-label uses).

201. *See, e.g.*, Peter Huber, *FDA Caution Can Be Deadly, Too*, WALL ST. J., July 24, 1998, at A14 (suggesting that the entire regulatory process is not needed to ensure that companies engage in responsible testing of drug products because "[n]o private company prospers for long selling products that kill, maim, or injure," and therefore rational drug companies will engage in sufficient research of their products without political prodding).

manufacturer to submit a supplemental application for off-label use,[202] effectively mandating that the manufacturer follow its off-label marketing programs with the standard research procedures that would apply to a new drug.[203] The statute also provides, however, for exemption from the supplemental application requirement,[204] which can be granted if the Secretary finds that "it would be economically prohibitive with respect to [the drug] . . . for the manufacturer to incur the costs necessary for the submission of a supplemental application."[205] The exemption provision purportedly ensures that certain off-label applications are not systematically denied marketing privileges simply because the manufacturer is very small or follow-up studies are highly complex and expensive.[206]

D. *Disclosure Requirements*

When the manufacturer sends authorized information to any of the qualified groups, it must include prominently displayed caveats disclosing that "the information concerns a use of a drug or device that has not been approved or cleared by the Food and Drug Administration."[207] The manufacturer also must enclose official labeling and labeling updates along with the authorized information.[208]

The legislation's disclosure requirements also address the importance of communicating possible sources of research bias to recipients of off-label promotional materials. Manufacturers must identify sources of

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202. *See* 21 U.S.C. § 360aaa-3(a) (1997).

203. The Prescription Drug User Fee Act of 1992, the provisions of which were extended in the Modernization Act of 1997, helps reduce bureaucratic impediments that once plagued drug application processes. The statutory provisions charge manufacturers "user fees" at certain stages in the marketing of their products, which revenues go toward hiring greater numbers of professionals to process new drug applications. *See* Prescription Drug User Fee Act of 1992, P.L. 102-571, 106 Stat. 4491 (1992) (codified as amended at 21 U.S.C. § 379g (1997)).

The User Fee Act (U.F.A.) expedites the processing of both new drug applications and supplemental applications. As a result, drug manufacturers that want to engage in off-label marketing may find the supplemental application requirement less daunting, or less of a disincentive, than under the previously more cumbersome time-frames. *See* Jill Wechsler, *Labeling's Ebb and Flow*, PHARM. EXEC., Feb. 1997, at 20. ("An important . . . accomplishment of FDA's user-fee program over the past four years has been to eliminate the backlog of old supplemental applications and to accelerate the review of new ones.").

204. *See* 21 U.S.C. § 360aaa-3(d)(1) (1997).

205. *Id.* § 360aaa-3(d)(2).

206. *See Changes for Marketers*, PHARM. EXEC., Dec. 1997, at 42 ("The agency [FDA] is most likely to agree to an exception when the sponsor is very small or the required study is very complex and expensive to conduct.").

207. 21 U.S.C. § 360aaa(b)(b)(A)(i) (1997).

208. *See id.* § 360aaa(b)(b)(A)(iv).

funding for the research.[209] Moreover, when applicable, they must disclose the fact that they are paying for dissemination of the information.[210] Finally, manufacturers must disclose the existence of any of a group of enumerated potential conflicts of interest pertaining to the authors of the information.[211]

The dissemination requirements also operate to ensure that the presentation of information be complete, and not slanted or skewed in favor of the manufacturer's promotion of a particular off-label use. The information must be accompanied by a bibliography listing other reference publications or journal articles concerning the use of the drug at issue.[212] Moreover, the Secretary has the power to determine that the information submitted by the manufacturer "fails to provide data, analyses, or other written matter that is objective and balanced."[213] In this event, the Secretary can notify the manufacturer of the determination and require the manufacturer to disseminate either or both of two additional things: additional objective, scientific information needed to provide balance, and a statement by the Secretary regarding safety and effectiveness of the off-label use.[214]

E. *Corrective Actions*

The legislation provides a final safeguard by authorizing "corrective actions" through which dissemination of off-label information can be halted. Under the provisions, after the manufacturer begins disseminating information, it must submit to the Secretary "a notification of any additional knowledge of the manufacturer on clinical research or other data that relate to the safety or effectiveness of the new use involved."[215] If the Secretary determines from the data that the use may be ineffective or significantly risky to public health, he or she can issue an order to cease dissemination.[216] The Secretary also can order cessation of dissemination if a manufacturer fails to comply with various statutory requirements,[217] or if problems exist pertaining to the supplemental application[218] or its

209. *See id.* § 360aaa(b)(b)(A)(vi).

210. *See id.* § 360aaa(b)(b)(A)(ii).

211. *See id.* § 360aaa(b)(b)(A)(iii). Specifically, the manufacturer must provide "the name of any authors of the information who are employees of, consultants to, or have received compensation from, the manufacturer, or who have a significant financial interest in the manufacturer." *Id.*

212. *See id.* § 360aaa(b)(b)(B).

213. *Id.* § 360aaa(c).

214. *See id.*

215. *Id.* § 360aaa-4(a)(2).

216. *See id.* § 360aaa-4(a)(1).

217. *See id.* § 360aaa-4(b)(1).

218. *See id.* § 360aaa-4(b)(2).

exemption.[219]

Overall, the legislation that ultimately passed was viewed by President Clinton as a compromise between two conflicting considerations.[220] The need to enhance access to drugs and medical devices, by giving professionals greater access to information regarding them, was balanced with a desire for safeguards sufficient to protect the welfare of consumers.[221] While the changes permit manufacturers to engage in off-label marketing of drugs for the first time in recent years, critics consider the statute's safeguards burdensome and inhibiting.[222] Yet despite the concern over bureaucratic hurdles that are built into the legislated process,[223] the off-label sections of the Modernization Act are among the statute's more revolutionary provisions.[224]

IV. POLICY RECOMMENDATIONS REGARDING OFF-LABEL PROCESSES

The preceding Parts have examined the nature of various off-label practices, considered the arguments that have been made by supporters and detractors of the practices, and examined the recent legislative modifications concerning off-label marketing. What remains is to consider solutions to the issues that have been raised, and make policy recommendations for Congress and the FDA as they continue to wrestle with all sides of this challenge.

The ideological debate over off-label practices can be synthesized into a few essential observations and recommendations: (A) Off-label prescription is an essential part of modern medicine, without which state-of-the-art advances would be intolerably retarded; (B) Although the social value of off-label prescription is mitigated by offsetting risks, restriction of off-label prescription or the marketing of off-label applications is not the best means of reducing these risks; (C) Off-label practices should be liberated from most extant legislative and regulatory constraints, subject to the following protective mechanisms: (1) full disclosure to physicians; (2) full disclosure to patients; and (3) retrenchment from some tort-reform measures that may reduce manufacturers' incentives to test for safety of

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219. *See id.* § 360aaa-4(b)(3).

220. *See Critics Question FDA Reform, Say Law Will Benefit Big Firms; Obstacles to Off-Label Info Use*, MED. MKTG. & MEDIA, Dec. 1997, at 22.

221. *See id.*

222. *See So What?*, *supra* note 105 ("With such restrictions [as the Modernization Act places on off-label promotions], some product company executives are asking, where's the reform?").

223. *See id.*

224. This conclusion is based on the fact a good number of statutory modifications of the Modernization Act essentially codify FDA regulations and practices that already were in place. For examples, see Salbu, *supra* note 13.

off-label uses and market off-label uses honestly and accurately.

A. *Off-Label Prescription Is an Essential Part of Modern Medicine, Without Which State-of-the-Art Advances Would Be Intolerably Retarded*

Whatever costs, risks, or other disadvantages might be associated with off-label prescription of drugs, two facts appear to be indisputable. First, some of the most effective drug treatments in existence today are off-label treatments.[225] Suppose we denied HIV and AIDS patients access to combination therapy until the combinations were tested and approved under the procedures the FDA uses for new drugs. Thousands of patients who have thrived using the unapproved cocktails would have met the same fate as patients before the advent of protease inhibitors—they would have deteriorated quickly, suffered terrible illnesses, and died.[226]

Second, off-label prescription creates unique opportunities to witness the effects of new applications over the widest possible population and during the shortest possible period. Unfettered access to an entire population of patients provides an unrestricted, admittedly informal laboratory, thereby hastening medical advances. Again, the case of off-label combination therapies for HIV and AIDS patients is exemplary. The costs and benefits of combination treatments will be revealed more quickly among the universe of patients than among a small sample of patients, and by a wide array of doctors rather than a handful of scientific investigators. Off-label prescription thus maximizes information and increases the speed with which it is amassed. Likewise, it multiplies the number of minds that will look at the information, apply different perspectives, and develop hypotheses, theories, and principles regarding a new treatment. The logical result of these dynamics should be to propel the state of the art of medical practice.

Of course, the arguments in Subpart II.C.2. remind us that the advantages of off-label prescription come at a cost. Indeed, critics simply look at the same half glass of water and describe it from a different perspective. Proponents extol speed, contending it gives patients access to effective new treatments and advances medical knowledge; opponents rebuke speed, arguing it puts patients at risk from harmful, unproven new treatment applications. Whether speed is good or bad depends on whether the treatment that is hastened turns out to be good or bad. The following Subpart addresses this problem, suggesting that the substantial benefits of

225. *See supra* Subpart II.C.1.a.

226. *See* Linda C. Fentiman, *AIDS as a Chronic Illness: A Cautionary Tale for the End of the Twentieth Century*, 61 ALB. L. REV. 989, 990-91 (1998) (noting role of protease inhibitors in extending lives of HIV and AIDS patients).

off-label prescription—and by extension, of off-label marketing—cannot be discarded. It also argues that the risks and costs of the practices must be addressed rather than ignored, but without recourse to a ban or quasi-ban that chills public discourse regarding scientific and medical information.

B. *Although the Social Value of Off-Label Prescription Is Mitigated by Offsetting Risks, Restriction of Off-Label Prescription or the Marketing of Off-Label Applications Is Not the Best Means of Reducing These Risks*

The benefits of off-label prescription are compelling enough to support two observations. First, we should not prohibit off-label prescription practices if there are any less restrictive means of reasonably protecting the public's interest in safety. Second, because off-label prescription is crucial to the effective treatment of patients and the advancement of medicine, communications regarding off-label practices should be considered crucial by extension. The ability of off-label applications to achieve their potential depends upon the rapid dissemination of information throughout the medical community.

These observations suggest that we should try to protect the public without banning off-label medical applications or chilling discussion of them. This challenge calls for creative, nontraditional solutions. The recommendations in the following Subpart minimize regulatory intervention and maximize exploitation of market forces as a relatively unintrusive method of public protection.

A couple of observations must be made regarding these less restrictive alternatives. First, because they protect the public in a different manner than direct legislative and regulatory bans, some of the specific beneficiaries and victims will change. People whose health would be spared by a ban might die under a market forces approach. Likewise, people who might die under a ban might be spared under a market forces approach. This simply reflects the fact that different methods attack the problem differently, and the winners and losers under alternative systems will not always be the same people.

Second, I propose a market-based approach under the belief that, *ceteris paribus*, more lives and health will be preserved than under the regulatory system presently in place. It is possible, perhaps even likely, that the alternatives proposed will provide less public protection against the risks of off-label prescription and marketing than stringent bureaucratic controls. Even if a degree of protection is sacrificed, the invaluable benefits of off-label practices outweigh some loss in the preservation of public safety from unproven applications. As in the preceding paragraph, the individuals who gain and lose under the existing approach and under my approach often will vary. I suggest only that the proposed method is likely to

increase the number of winners over losers.

C. *Off-Label Practices Should Be Liberated from Most Legislative and Regulatory Constraints, Subject to Several Protective Mechanisms*

All three off-label practices identified in Part II—off-label use, off-label prescription, and off-label marketing to physicians—should be broadly permissible and free from bureaucratic constraint. This means that use and prescription should remain legally and socially accepted practice, and that marketing of off-label applications should be unfettered from some of the more burdensome, less justifiable restrictions contained in the Modernization Act.

Not all of the Act's provisions are dysfunctional. The restriction of off-label marketing to qualified professional groups is reasonable, particularly given the relative breadth of recipients under the provisions.[227] Other justifiable provisions of the Act are largely those that support market force protections by increasing available information through disclosure requirements. For example, requiring manufacturers to disclose that an off-label application hasn't been approved by the FDA[228] is easy, inexpensive, and useful. Disclosure of funding sources[229] likewise is easy to do and serves a potentially important function. Indeed, disclosure of information is so central a part of market-based protection that I recommend additional disclosure requirements in Subparts IV.C.1. and 2. below.

Other disclosure requirements are at least somewhat more onerous to manufacturers, and while they do serve useful informative functions, they are a bit more controversial because they add a moderate hurdle to off-label marketing endeavors. I refer here to the requirements to provide bibliographies of other reference publications and journal articles on a subject,[230] and to provide on request of the Secretary balanced, objective, scientific information regarding an off-label use.[231]

While these disclosure requirements impose preparation, labor, and therefore costs on manufacturers, these burdens are ultimately justifiable. A manufacturer exercising reasonable care in creating its marketing materials will do a methodical search of the literature, ascertain that it has seen all relevant findings, and weigh conflicting findings carefully before promoting a particular off-label use. Since all these activities are essential

227. Qualified recipients include health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and federal and state governmental agencies. *See supra* note 185 and accompanying test.

228. *See supra* note 207 and accompanying text.

229. *See supra* note 209 and accompanying text.

230. *See supra* note 212 and accompanying text.

231. *See supra* note 215 and accompanying text.

to reasonably careful marketing efforts, we can assume that reporting the information is simply pro forma for any responsible company.

A number of the Act's other restrictions, however, create such cumbersome hurdles to the dissemination of information that companies are likely to forego promoting innovative uses of FDA-approved drugs. Taken together, these requirements will discourage companies from disseminating potentially valuable information about their products. Unjustifiable impediments include the supplemental application requirement and the authorized information restriction.

The supplemental application provision of the Modernization Act requires companies that are not exempted to file a supplemental application or a certification of intent to submit a supplemental application in order to begin off-label marketing.[232] This is a substantial bureaucratic hurdle, potentially capable of rendering the off-label marketing provisions of the Act virtually inoperative. While the provisions would indeed ensure that companies investigate off-label applications, they are burdensome and unnecessary. The market-oriented alternatives recommended later in this Part can substitute effectively for the supplemental application requirement. Retrenchment from the irrational tort reform measure of punitive damage caps will establish effective manufacturer incentives to act responsibly and investigate off-label uses. Stepped-up disclosure requirements will empower both professionals and patients to make informed decisions regarding any residual risks that cannot be eliminated.

The authorized information restriction systematically disqualifies potentially valuable research from being the subject of off-label promotions. A company cannot inform doctors about respectable and informative findings published in a peer-reviewed journal not indexed in the Index Medicus.

This chilling effect is unnecessary. Since we are limiting the liberation of off-label marketing to efforts aimed at physicians and other qualified health professionals, we are restricting the flow of information to a select and highly educated group. They are capable of collecting information on all sides of an issue. Moreover, methods are available to encourage manufacturers to monitor themselves and restrict their efforts to responsible promotion activities. The ways in which doctors and manufacturers can be encouraged to act responsibly, thereby shielding patients from irresponsibility, are discussed below.

1. Full Disclosure to Physicians

In Part III, we observed that a number of the provisions of the Modernization Act are intended to compel pharmaceutical companies to

232. *See supra* Subpart III.C.

provide balanced, complete disclosure in their off-label marketing practices. Under the legislation, manufacturers must inform recipients of a promotion that the information concerns an off-label use.[233] They must include labeling information with the promotion,[234] identify sources of funding for the research being cited,[235] disclose any conflicts of interest to which the authors of the information may be subject,[236] and disclose the fact that the manufacturer is paying for the information's dissemination.[237] Finally, the promoting manufacturer must provide a bibliography listing other reference publications or journal articles regarding the use of the drug being promoted,[238] and otherwise provide data and materials that are "objective and balanced."[239]

These requirements are prudent. They help ensure that medical professionals get a reasonably complete picture of the benefits and risks of an off-label use, to the extent that they are known. The statutory requirements place only a minor burden on manufacturers, which should not be unduly expensive or time-consuming. Moreover, the requirements reflect the kinds of activities that any careful manufacturer should undertake before recommending an off-label use. For example, what prudent manufacturer would recommend an unapproved use of a drug on the basis of a single study, and decline to find and examine other studies that might contradict the favorable research? It hardly seems burdensome to require the manufacturer to find the body of research concerning an off-label use and provide it to the recipients of its off-label marketing efforts.

2. Full Disclosure to Patients

We noted earlier that, under the learned intermediary doctrine, physicians serve as a protective layer between manufacturers of prescription drugs and the patients who take those drugs.[240] Within this system, manufacturer labeling is directed to physicians rather than to patients, and physicians exercise broad discretion in terms of the kinds of relationships they establish with their patients.[241] Within the boundaries of

233. *See* 21 U.S.C. § 360aaa(b)(b)(A)(i) (1997).
234. *See id.* § 360aaa(b)(b)(A)(iv).
235. *See id.* § 360aaa(b)(b)(A)(vi).
236. *See id.* § 360aaa(b)(b)(A)(iii).
237. *See id.* § 360aaa(b)(b)(A)(ii).
238. *See id.* § 360aaa(b)(b)(B).
239. *Id.* § 360aaa(c).
240. *See supra* note 31 and accompanying text.
241. Of course, a relationship takes two, and patients can play a role in determining the part they will play in their treatments. Nonetheless, given that the doctor is the professional, that patients can be intimidated by the context they are in and their relative ignorance, and that the doctor has a home field relational advantage, we would expect doctors ordinarily to play the dominant role in

acceptable medical practice, doctors can keep patients highly informed and make patients active decision-makers in the course of their treatment.[242] Likewise, doctors can adopt a more controlling posture, under which the patient is treated like an object to be passively processed and fixed.[243] Because the patient-as-object model has become so prevalent, many patients have grown to expect doctors simply to administer treatments and provide palliatives or cures.[244] Indeed, the autonomy of doctors in fashioning legally acceptable doctor-patient relationships is so broad that omission to inform patients that their treatments are off-label treatments is a common, lawful practice.[245]

Given the advanced state of medical practice and the complexity of medical information, some degree of physician discretion in patient treatment is unavoidable. In this context, however, it is hardly surprising that a bureaucratic structure has developed to protect patients from harmful and unproven treatments. Nonetheless, at least some administrative patient protections, in the form of FDA rules and regulations, might logically be replaced by augmenting the amount and kinds of information given to patients, and then shifting more responsibility onto them to make treatment decisions in their own best interest.

When there is serious opposition to an administrative approach to consumer protection, it therefore makes sense to try to find ways to replace the objectionable regulations with increased consumer disclosure and increased consumer autonomy in making potentially difficult choices. In the case of off-label practices, the interests of free speech and medical advancement support this approach. Other recommended protections in this Part should encourage both manufacturers and doctors to restrict their off-label practices to responsible ones. Once these mechanisms are in place to limit the kinds of off-label practices likely to pervade the marketplace,[246]

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defining the physician-patient relationship.

242. *See* Carl E. Schneider, *Bioethics With a Human Face*, 69 IND. L.J. 1075, 1087 (1994) (discussing patient sovereignty and the role of patient as an active participant in determining the course of treatment).

243. For a chilling description of a patient being processed by the medical establishment, see DIANE JOHNSON, HEALTH AND HAPPINESS (1990).

244. *See* Vernellia R. Randall, *Managed Care, Utilization Review, and Financial Risk Shifting: Compensating Patients for Health Care Cost Containment Injuries*, 17 PUGET SOUND L. REV. 1 (1993).

245. *See supra* notes 57-58 and accompanying text.

246. The effectiveness of informed decision-making and consent as a substitute for regulatory protections depends on the implementation of the other measures recommended in this Part, or alternative measures that achieve the same ends. Informing patients and then shifting to them the right and responsibility to direct their treatments will not protect patients from drugs that are prematurely marketed. If drugs are marketed too early, patients will be forced to make decisions based on disclosure that the risks are unknown, and some risk-prone patients will be harmed. Accordingly, disclosure and consent elements of the proposed reform must be supported by

it is time to shift decision-making authority to informed patients. This is best achieved by requiring doctors to tell patients that their off-label treatments have not been approved by the FDA, to explain the known risks and potential benefits, and then to permit the patients to decide whether to undertake a treatment. In addition to supporting the commercial speech rights of manufacturers and the efficient progress of medical advancement, this approach empowers patients and erodes what can be an insultingly paternalistic institution that treats patients more as objects than as active participants in their own treatments.

3. Retrenchment from Some Tort-Reform Measures that May Reduce Manufacturers' Incentives to Test for Safety of Off-Label Uses and Market Off-Label Uses Honestly and Accurately

I have suggested that the interests of free speech and medical progress outweigh patient safety concerns in the off-label marketing debate, at least if measures other than a marketing ban can mitigate consumer risks. It bears remembering, however, that the concerns identified by off-label marketing opponents are legitimate and serious. Whenever we try to hasten patient access to new treatments, we do so at the risk of exposing patients to undiscovered dangers.

The pharmaceutical companies wishing to market their products without interference express compelling First Amendment rights that should not be denied. Given the potential costs and dangers of off-label promotion, however, the companies must take responsibility for their marketing endeavors. Realistically, this responsibility translates into tort liability for incomplete product testing, premature product distribution, and off-label product promotion based on incomplete or unreliable data. The message is simple—if you want to promote what have been accurately cast as experimental uses of FDA-approved drugs,[247] be prepared to pay in the event that you fail to exercise reasonable care in doing so.

Of course, liability cannot undo a serious physical injury or death. The knowledge that liability is imminent will serve, however, to deter companies from premature or inaccurate off-label promotion activities, thereby lowering the instance of irresponsible marketing tactics. Ordinary tort liability, in the form of compensatory damages awarded for negligence, is of course one potential deterrent to carelessness in promotion activities. In addition, a rigorous punitive damages policy can go far to ensure manufacturer diligence.

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incentives such as manufacturer liability policies that hold pharmaceutical companies accountable for their actions.

247. *See supra* Subpart II.C.2.b.

Specifically, some recent irrational components of tort reform[248] should be modified to give manufacturers compelling incentives to exercise care in creating fair, balanced, and responsible advertising campaigns. Unjustifiable constraints on punitive damage awards, in the form of statutory caps or ceilings,[249] should be abandoned.[250] In states where punitive damages are limited to a few hundred thousand dollars, regardless of the severity of a defendant's wrongdoing,[251] manufacturers may believe they can act irresponsibly with relative impunity. This social condition is intolerable, as is any social condition in which liberty is unaccompanied by responsibility for one's actions. If drug manufacturers want the freedom to market off-label uses of their products, they should accept potentially strict punitive consequences if they abuse that freedom.

Of course, the standard for civil punishment must be high—punitive damages should be awarded only in instances of gross negligence, recklessness, malice, intent to harm, or extreme and outrageous behavior. Infliction of punitive damages for behaviors less egregious would be unfair and would discourage the marketing of off-label applications that can be so valuable to patients and to medical advancement. Sensible liability policies should grant full compensation for negligent marketing practices, and uncapped punitive damages, commensurate with wrongdoing, for more culpable marketing practices. If manufacturers are subjected to these sanctions, both they and society at large can benefit from unconstrained license to market off-label applications responsibly.

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248. While arguments are made on both sides of the tort reform issue, persuasive evidence suggests that the liability crisis and out-of-control jury awards have been largely exaggerated. *See, e.g.*, Brian T. Beasley, *North Carolina's New Punitive Damages Statute: Who's Being Punished, Anyway?*, 74 N.C. L. REV. 2174, 2190 (1996) (citing findings that recent punitive damage awards have been modest in North Carolina); Steven Daniels & Joanne Martin, *Myth and Reality in Punitive Damages*, 75 MINN. L. REV. 1, 31 (1990) (noting data suggesting infrequency of punitive damage awards in civil cases); Michael L. Rustad, *Nationalizing Tort Law: The Republican Attack on Women, Blue Collar Workers and Consumers*, 48 RUTGERS L. REV. 673, 694-95 (1996) (noting reasonableness of amount and frequency of punitive damages awards).

249. I label statutory ceilings on punitive damages as unjustifiable because the caps have no bearing on culpability, but are either arbitrary figures or multiples of compensatory damages that bear no relationship to the function of punishment. For elaboration of the argument that the ceilings are dysfunctional, see Steven R. Salbu, *Developing Rational Punitive Damages Policies: Beyond the Constitution*, 49 FLA. L. REV. 247, 297-300 (1997).

250. These constraints are unjustifiable throughout the economy and should be abandoned in general, and not just in conjunction with grossly negligent marketing of off-label applications. Off-label marketing abuses are just one example of how justifiably strong punitive damages policy can allow us to reduce or eliminate government regulation, by creating market incentives for self-policing behavior.

251. *See, e.g.*, VA. CODE ANN. § 8.01-38.1 (Michie 1987) (capping punitive damages in Virginia at $350,000).

V. CONCLUSION

The recommendations in Part IV have been shaped by an overarching, synthesizing philosophy. Along the lines of First Amendment jurisprudence, the philosophy begins with the premise that, while commercial speech regulations need not necessarily comprise the least restrictive alternative of advancing legitimate government interests, they also cannot be more burdensome than necessary.[252] Accordingly, the interests of doctors and patients in the most rapid diffusion of knowledge concerning new off-label applications must not be unduly impaired. Mechanisms to protect patients from the risks of aggressively marketed off-label uses should respect the free flow of information.

These mechanisms should protect the public by requiring full disclosure to both doctors and patients, and by holding professionals accountable for the ramifications of their actions. The proposals that were discussed in Part IV empower all parties involved—manufacturers, physicians, and patients—by optimizing the information available to, and in some instances mandated for, each group. The provider groups—the manufacturers and the doctors—are then encouraged, through exacting liability policies, to use the information responsibly to protect patients.

Critics of off-label practices in general, and of off-label promotion practices specifically, may suggest that these liberalizations, which would substantially exceed the federal statutory changes of 1997, will come at the cost of some lives. Indeed, it is very likely that some people who would be protected from risky off-label applications under more restrictive laws will be subjected to them under the proposed approach. It is also inevitable that in some cases, the off-label applications to which they are exposed will be dangerous and even deadly. Accordingly, some people very likely will be exposed to products from which they would have been protected under more stringent regulations. Some will suffer heartbreaking loss of health or of life as a result.

The safeguards I propose—open information access and liberal liability policies—can avert only some of these hazards. Activists who would restrict off-label practices aggressively must recall, however, that the aforementioned costs must be balanced against the benefits to be gained from liberalized off-label practices. As noted in Part II, much of the state of the art in medical practice consists of, or first was introduced through, off-label applications of FDA-approved drugs. The proposals in this article recognize the tremendous importance of medical progress, as well as the role of off-label practices in fostering this progress. Accordingly, while the

252. *See* United States v. Edge Broadcasting Co., 509 U.S. 418, 430 (1993).

consumer protections proffered are not as stringent as possible, they are justifiable and indeed necessary in light of the benefits of off-label applications.