

Before the  
Food and Drug Administration, HHS  
Rockville, MD 20857

In the Matter of                    )  
Request for Comment            )  
On First Amendment Issues    )                    Docket No. 02N-0209

Comments of  
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These comments are submitted in response to FDA's May 16, 2001 *Federal Register* notice<sup>1</sup> requesting comments on how FDA can assure that its controls over commercial speech and other speech by regulated firms conforms to recent Supreme Court decisions on the application of the First Amendment. My comments pertain only to pharmaceuticals, not foods or cosmetics.

FDA was given authority over prescription drug advertising and promotion in the 1962 amendments to the Food, Drug and Cosmetics Act. In the following decades, FDA developed its regulation of commercial speech by pharmaceutical firms with little if any attention to the First Amendment protections for commercial communications that emerged from the Supreme Court's 1975 *Virginia Pharmacy* decision and later cases. As I argue below in the section on "leverage," the institutional setting in which FDA advertising regulation occurs has forestalled legal challenges by manufacturers. At the

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<sup>1</sup> 67 *Fed. Reg.* 34942, May 16, 2002

same time, FDA has strong incentives to construct very strict regulations so as to insulate the staff from criticism for possibly inappropriate advertising and promotion. This suggests that many of the core features of FDA's regulation of commercial speech and other communications by pharmaceutical manufacturers are probably far too stringent to be consistent with First Amendment law.

The few FDA regulations that have been challenged on First Amendment grounds have generally failed to withstand judicial scrutiny (*Pearson v. Shalala*,<sup>2</sup> *Washington Legal Foundation v. Friedman*,<sup>3</sup> and *Thompson v. Western States Medical Center*<sup>4</sup>). The verdicts in those lawsuits suggest, again, that many FDA regulations of prescription drug advertising would encounter problems if challenged on First Amendment grounds.

In the next section, I recommend three fundamental changes in how FDA approaches the regulation of commercial speech and information dissemination. A later section offers more detailed recommendations on specific aspects of FDA regulation.

## **Fundamental Changes in FDA Regulation of Commercial Speech and Information Dissemination**

### **1. Apply an Evidence-based Rule of Reason When Determining Whether Communications Are Misleading**

FDA advertising regulation is based on the statutory authority to prohibit false or misleading claims. Many of the agency's regulations are premised on an assessment that specific communications are inherently misleading. In making these determinations, however, FDA staff typically cite little or no evidence. Examples include FDA's requirements that advertisements contain detailed disclosures, and FDA's prohibition on

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<sup>2</sup> 164 F.3d 650 (D.C. Cir. 1999).

<sup>3</sup> 13 F. Supp. 2d 51 (D.D.C. 1998). *extended sub nom. Washington Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part*, 202 F.3d 331 (D.C. Cir. 2000).

<sup>4</sup> 122 S. Ct. 1497 (2002).

the dissemination of so-called off-label information (pertaining to findings not listed in FDA-approved labeling). For reasons discussed below, these regulations have never been challenged by manufacturers on First Amendment grounds. When other parties challenged these regulations in the past few years, however, the courts refused to countenance FDA's assumptions, in the absence of evidence, that these commercial communications are inherently misleading (again, see *Pearson v. Shalala*, *Washington Legal Foundation v. Friedman*, and *Thompson v. Western States Medical Center*). Also relevant is the history of Federal Trade Commission (FTC) litigation, in which the courts have often refused to accept staff assessments on whether advertisements are misleading, especially when the staff reached their conclusions in the absence of extrinsic evidence. In particular, the courts have generally found that FTC should consider empirical evidence if it is offered by litigants.<sup>5</sup>

I recommend that FDA operate on the assumption that the courts would adopt a similarly critical posture toward the plethora of unchallenged FDA regulations that rely upon unsupported determinations that communications are misleading.

To avoid having the courts strike down many of these regulations, FDA should cease making what are essentially *per se* conclusions that certain communications are inherently misleading. Instead, FDA should take into account the information environment in which communications occur and the manner in which recipients judge and use information from commercial sources. Among the relevant considerations is the obvious fact that physicians have access to, and commonly use many information sources including journals; textbooks; practice guidelines and other materials from the National Institutes of Health and other prestigious sources; continuing medical education; discussions with colleagues; and conferences.<sup>6</sup> Also relevant is the fact that audiences do

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<sup>5</sup> Some of this history and the relevant FTC policies are described in the FTC's 1983 "Policy Statement on Deception" and its 1984 "Advertising Substantiation Policy Statement," and in Ford and Calfee 1984. For a more recent view, see Beales and Muris 1993.

<sup>6</sup> On the apparently strong influence of the publication of results from landmark clinical trials for the statin class of cholesterol-reducing drugs, see Mamdani and Tu

not treat these sources equally. Research has found that consumers in general, and physicians in particular, pay attention to the credibility of information sources, especially self-interested sources such as advertisers. Consumers tend to assume that advertising is not credible in the absence of specific information to provide a basis for credibility (Calfee and Ringold 1994). Physicians rate pharmaceutical firms very low in trustworthiness compared to other information sources. In representative survey of oncologists, for example, peer-reviewed journals were rated as “highly credible” sources by 79% of respondents, compared to 45% for practice guides from government, 33% for consultation with colleagues, and 10% for pharmaceutical detailers (Calfee and McGinnis 1997, Thakker 1997).

These findings on source credibility have strong implications for the treatment of DTC advertising of prescription drugs and promotion directed at physicians, both of which are discussed below.

## **2. Replace Most *per se* Bans with a Mix of Disclosures and Safe Harbor Standards**

The application of an evidence-based rule of reason would almost certainly call into question the validity of FDA’s current policy of enforcing outright bans or near-bans on many types of communications without any evidence that the communications would be misleading or harmful. FDA regulations list approximately twenty advertising elements deemed *per se* “false, lacking in fair balance, or otherwise misleading.”<sup>7</sup> The regulations also list some thirteen additional types of communications that “may be false, lacking in fair balance, or otherwise misleading.”<sup>8</sup> For example, manufacturers are warned against failing “to provide adequate emphasis ... for the fact that two facing pages are part of the same advertisement when one page contains information relating to

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2001.

<sup>7</sup> 21 C.F.R. § 202.1(e)(6).

<sup>8</sup> 21 C.F.R. § 202.1(e)(7).

side effects and contraindications.”<sup>9</sup> FDA also prohibits advertising claims about differences between brand-name and generic drugs that the FDA has concluded are therapeutically equivalent.<sup>10</sup>

Recent court decisions on commercial speech restrictions in other markets, and on FDA's restrictions on commercial speech about both foods and drugs, make clear that *per se* bans are unlikely to survive a First Amendment challenge if regulators do not provide persuasive reasons why the banned speech is false or misleading.<sup>11</sup> Because FDA seems to have accumulated little if any evidence in support of the many bans that have not yet been challenged, the bans are open to attacks on at least two grounds: (a) the information being communicated is not inherently misleading, and thus should be subject to a rule of reason assessment based on evidence (as would be the case in FTC litigation); and (b) simple disclosures could prevent significant deception. The Supreme Court has given considerable emphasis to the latter point, noting that disclosures are almost always to be preferred to an outright ban:

Because the extension of First Amendment protection to commercial speech is justified principally by the value to consumers of the information such speech provides, appellant’s constitutionally protected interest in *not* providing any particular factual information in his advertising is minimal. Thus, in virtually all our commercial speech decisions to date, we have emphasized that because disclosure requirements trench much more narrowly on an advertiser's interests than do flat prohibitions on speech,

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<sup>9</sup> 21 C.F.R. § 202.1(e)(7).

<sup>10</sup> 54 F-D-C REP. (“The Pink Sheet”), July 13, 1992, p. 8.

<sup>11</sup> See, e.g., *Ibanez v. Florida Dep’t of Bus. and Prof’l Regulation*, 512 U.S. 136, 146 (1994) (“[W]e cannot allow rote invocation of the words ‘potentially misleading’ to supplant the [government’s] burden . . . .”); *In re R.M.J.*, 455 U.S. 191 (1982) (speech at issue “has not been shown to be misleading”); *Washington Legal Found. v. Henney*, 56 F. Supp. 2d 81, 85 (D.D.C. 1999) (“FDA may not restrict speech based on its perception that the speech could, may, or might mislead.”), *dismissed and vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000); *Pearson v. Shalala*, 164 F.3d 650, 655 (1998) (rejecting argument that health claims were inherently misleading based on lack of “significant scientific agreement”).

“warning[s] or disclaimer[s] might be appropriately required ... in order to dissipate the possibility of consumer confusion or deception.”<sup>12</sup>

I recommend that FDA reassess all bans on specific communications, in order to determine (1) whether these communications are in fact nonmisleading after taking into account the information environment in which the communications occur; and (2) whether communications that are still thought to be misleading can be acceptably qualified by disclosures. In considering the role of disclosures, FDA should consider whether communications can avoid misleading consumers or physicians by specifying the nature of the evidence underlying claims. A policy of permitting suitably qualified claims would permit the public to take advantage of useful findings that rely upon evidence that falls short of FDA standards for approving new drugs and supplemental indications for approved drugs.

As the courts have also noted, however, requirements on the content and placement of disclosures can be so stringent as to render claims infeasible and thus essentially banned. That was the situation for broadcast advertising directed at consumers before FDA's 1997 reinterpretation of its regulation (Pines 1999). Below, I discuss how disclosure requirements can be shaped to bring them into compliance with First Amendment law.

### **3. Reduce Inappropriate Regulatory “Leverage” to an Acceptable Level**

Even if FDA were to adopt the changes just recommended -- using evidence rather than intuition for assessing whether communications are misleading, and avoiding *per se* bans wherever possible -- these changes would probably not bring the bulk of FDA's regulation of commercial speech and information dissemination into substantial compliance with modern First Amendment law. The innumerable judgments required for such changes would be made by FDA staff who presumably believe that current regulations, including bans, are necessary. More important, the staff may expect these

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<sup>12</sup> *Zauderer*, 471 U.S. at 651 (quoting *In re R.M.J.*, 455 U.S. at 201) (internal citations omitted).

regulations to remain unchallenged by litigation for many years, regardless of how slowly or incompletely the regulations are altered to bring them into conformity with First Amendment law. This is because FDA staff must be aware that in the four decades in which it has exercised authority over pharmaceutical advertising and promotion, FDA developed its prescription drug advertising regulations without a single legal challenge from manufacturers. This history has been emphasized by FDA staff itself (Fisherow, 1987, p. 230):

No federal court has yet been put in a position to issue an opinion construing the meaning or application of the provisions of section 502(n) of the Food, Drug, and Cosmetic Act in an advertising case. This capacity to resolve difficulties to its satisfaction before they reach the courts has delivered what FDA wants most, the prompt cessation or transformation of a questioned advertising claim or campaign, with a relatively modest expenditure of resources.

Fisherow also noted that of several thousand advertising enforcement letters sent out during 1971-1983, only 17 rose to the level of “regulatory letters,” the strongest warnings sent by the staff to firms. Another member of FDA's advertising regulation division, writing at the same time (Yellin 1987), counted only four regulatory letters during the previous six years. Clearly, FDA has been able to obtain compliance with its extraordinarily detailed advertising regulations without resorting to litigation or facing litigation by manufacturers.

The reason for the absence of legal challenges to FDA advertising regulation appears to be “leverage,” i.e., the exceptional power possessed by FDA staff because the firms they regulate are simultaneously subject to FDA regulation of virtually every aspect of their business, including new drug approvals and continuing approval of manufacturing facilities. Even a small probability of retaliation or unhappiness on the part of FDA staff is clearly sufficient to deter legal challenges to advertising regulations. This, too, has been noted by FDA staff (Fisherow, 1987, p. 231-232, notes eliminated):

One may speculate about why the Agency has been so successful [in regulating without legal challenge]. It may be that it is always correct in its analysis and persuasive enough in its communication to deter an advertiser from continuing to disseminate a questioned message. The more likely case is that the Agency is not

always right, but that it succeeds anyway because of the nature of its relationship with pharmaceutical advertisers.

The author then notes that unlike the situation with the Federal Trade Commission (which regulates advertising in most other markets):

. . . the FDA licenses the prescription drug products subject to its regulation and approves labeling which effectively sets the limits on what may be communicated about product performance. This pervasive involvement in the industry's current and future business means that a corporate decisionmaker needs to consider more than just the merits of the company's position in the particular advertising dispute at hand. The executive must also weigh how much disagreement with the FDA staff in a current matter might affect future treatment. No such continuing relationship exists between the FTC and any industry.

The author continues:

This is undoubtedly one reason why the FTC is often compelled to act formally in an adversary proceeding to achieve the regulatory results it seeks. Thus, we have a substantial body of administrative and judicial opinion built up over decades illuminating the application of sections 5 and 12 of the Federal Trade Commission Act to advertising practices. We have no similarly available case law to show us how FDA applies section 502(n) of its statute or to comfort us with the fact that the law may mean something other than what the Agency says it means.

I believe this analysis by a member of the FDA advertising regulation staff was, and remains, sound. A few years later, then Commissioner David Kessler endorsed this view when he wrote, “Companies interested in maintaining positive relationships with the FDA usually agree to the FDA's remedy [in advertising matters]” (Kessler and Pines 1990). The courts have recognized similar phenomena in other agencies, such as the Federal Communications Commission, with their ability to regulate by “raised eyebrows.”<sup>13</sup>

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<sup>13</sup> *MD/DC/DE Broadcasters Ass'n v. FCC*, 236 F.3d 13, 19 (D.C. Cir. 2000) (noting the possibilities for “a variety of *sub silentio* pressures and ‘raised eyebrow’ regulation”), *en banc denied*, 253 F.3d 732 (2001), *cert. denied*, 122 S. Ct. 920 (2002); *see also, e.g., Writers Guild of America, West, Inc. v. American Broadcasting Co., Inc.*, 609 F.2d 355, 365 (9th Cir.1979) (“Regulation through ‘raised eyebrow’ techniques or through forceful jawboning is commonplace in the administrative context, and in some instances may fairly be characterized ... as official action by the agency.”) (footnotes

I therefore think that in the absence of structural changes, FDA is unlikely to implement the most important changes in advertising regulation necessary to ensure reasonable compliance with First Amendment protections for commercial and non-commercial speech. One solution, which I have recommended elsewhere, would be to transfer regulation of prescription drug advertising back to the FTC, which regulated prescription drug advertising before 1962 and has always regulated advertising for over-the-counter drugs, medical devices, and health care services including physicians and hospitals (Calfee 2002). That solution would, of course, require new legislation.

Without legislation, however, FDA can make organizational changes that would substantially reduce the leverage problem just described, and thus increase the likelihood that manufacturers would bring courtroom challenges against advertising regulations that do not comply with First Amendment law. Advertising and promotion is regulated by the Division of Drug Marketing, Advertising, and Communications (DDMAC). This group is located within the Center for Drug Evaluation and Research (CDER), which approves new drugs and new uses for existing drugs, and among other things, reviews and approves all pharmaceutical manufacturing facilities and methods. The linkage among these various regulatory functions within CDER, and the concomitant ability to obtain compliance in one area through regulatory presence in another, is well known within the industry and has been remarked upon in news reports.<sup>14</sup> In contrast, as the above analysis by member of DDMAC indicates, FTC staff regulate only advertising and have no direct

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omitted), *cert. denied*, 449 U.S. 824 (1980); *Writers Guild of America v. FCC*, 609 F.2d 355, 365-66 (9th Cir. 1979) (noting that “the line between permissible regulatory activity and impermissible raised eyebrow harassment of vulnerable licensees is ... exceedingly vague”); *Consolidated Edison Co. v. FPC*, 512 F.2d 1332, 1341 (D.C. Cir. 1975) (“Regulation through ‘raised eyebrow’ techniques seems inherent in the structure of most administrative agencies, combining as they do both policy-making and adjudicative functions.”).

<sup>14</sup> This linkage is apparent in recent FDA initiatives in the regulation of manufacturing. See Petersen and Abelson (2002), who note “The agency has also begun holding up approval of new drugs until the companies can convince it that they have fixed manufacturing problems -- an action that gets investor attention quickly and can send the price of a company’s stock down.”

connection with government agencies regulating health and safety or other crucial aspects of the businesses subject to FTC advertising regulation. The result is that firms feel free to bring legal challenges to FTC advertising regulations, so that FTC policies must withstand judicial application of the First Amendment.

I therefore strongly recommend that DDMAC be transferred out of CDER to become a standalone entity that reports directly to either the General Counsel or the Commissioner. So far as possible, the new division should maintain an arms length relationship with CDER, somewhat as FTC staff do when they seek out or rely upon the expertise of CDER, other FDA divisions, and other authoritative organizations when it is appropriate to do so. FTC history clearly indicates that medical technology advertising can be regulated in a reasonable and efficient manner while maintaining a decisive separation from the entities that approve new products.

### **Specific Changes in FDA Regulation of Commercial Speech and Information Dissemination**

I also recommend several specific changes that can make FDA regulations less susceptible to First Amendment challenges.

#### **1. Changes in the Regulation of Direct-to-consumer (DTC) Advertising of Prescription Drugs**

FDA is to be commended for taking the initiative in August 1997 to reinterpret its regulations to permit branded advertising in broadcast media (cf. Pines 1999; Calfee 2002). In a forthcoming journal article (Calfee 2002), I summarize the empirical evidence on the effects of DTC advertising. Much of that evidence comes from representative national surveys commissioned by FDA and other organizations including *Prevention Magazine*. That evidence supports the following points: (1) Consumer survey results, along with the stringent nature of FDA regulation, largely rule out the possibility that DTC advertising causes systematic consumer deception. In particular, surveys fail to reveal a tendency for DTC advertising to downplay the risks of

prescription drugs. (2) DTC advertising provides valuable information to consumers about potential drug treatments, along with information on risks and side effects, thus increasing the salience of both risks and benefits from drug therapy.

(3) DTC advertising motivates consumers to seek additional information from physicians, pharmacists, and other sources. Between 14% and 27% of surveys respondents (in the 1999 *Prevention* and 1999 FDA surveys, with the 2002 FDA survey at 18%) said DTC ads caused them to ask their doctors about a medical condition they had not previously discussed. (4) From the patient's perspective at least, DTC advertising causes almost no tension in the doctor's office. A consistent finding is that very few respondents -- usually well under 5% -- encountered resentment or resistance when they brought up what they had seen in advertising, or asked about specific drugs, while overwhelming majorities said their physicians treated their questions as an ordinary part of office discussions.

(5) Large majorities of consumers (on the order of 60% to 80%) think DTC ads provide them with useful information and help them in talking to their doctors. (6) DTC advertising appears to yield significant spillover benefits that go to consumers rather than to advertisers. These benefits include greater awareness of the risky nature of pharmaceuticals; better compliance with drug therapies; and greater awareness of the benefits of life-style and behavioral changes in dealing with diabetes; elevated cholesterol; and other conditions that are the subject of DTC advertising.

Based on this analysis, I recommend several changes in FDA regulation of DTC advertising:

(1) FDA should reconsider its assumption that DTC ads should always contain a balance of information about risks and benefits. Consumers assume that information in ads is biased in favor of the advertiser (Calfée and Ringold 1994), so they expect ads to emphasize benefits. Consumers can turn to more objective sources for offsetting risk information, and the prescription requirement assures that patients will gain the benefit of a physician's expert advice before obtaining an advertised medicine. Rather than requiring advertisements to devote substantial resources to risk information, it makes

more sense for risk information to be targeted precisely at users. That would be the natural result of leaving physicians and pharmacists with the primary task of disseminating risk information when it is most needed, i.e., when the drug is prescribed and the prescription is filled. This arrangement would also permit advertising to focus on the difficult task of communicating to consumers that drug therapies are available for underdiagnosed and undertreated conditions. There is no reason to expect such an arrangement to work badly. The ability of consumer advertising to work well in other health care markets, despite the absence of detailed risk information in ads, is apparent in the markets for such sophisticated products as hospitals, clinics, physicians, and dentists.

(2) Regardless of whether FDA reassesses its broad requirement for balance in DTC ads, I recommend that FDA regulations be altered so that risk information in ads, especially in broadcasting, can be more strongly modulated according to relative risks of the advertised product. Except for drugs that pose unusual dangers, the primary risk information in advertisements could consist of an unmistakable statement to the effect that physicians will have something important to say about whether and how to use the drug. One benefit of this arrangement would be to increase the prominence of strong warnings in ads for the few drugs where risks are substantial and consumer vigilance is especially useful. Research by FDA staff in the 1980s found that relatively simple risk information was actually more effective than detailed warnings (Morris and Millstein 1984; Morris, Ruffner, and Klimberg 1985).

(3) I recommend that FDA permit DTC advertisements to contain reasonably qualified comparison claims.<sup>15</sup> Efficacy claims between two drugs are now virtually prohibited unless manufacturers conduct two clinical trials directly comparing the two drugs. This rule is enforced so tightly as to make comparisons among closely competing brands inordinately difficult. If FDA regulations were suitably altered, manufacturers of brands that compete with each other, but vary in precise efficacy and side-effects, could truthfully point out, for example, that Brand X antidepressant “may work as well for you

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<sup>15</sup> The rule against comparative claims is among the approximately twenty prohibited advertising elements or claims referred to earlier.

as Brand Y does, and it costs one-third less.” In most markets, comparison claims, including price claims, are an essential part of competition. Comparison claims could make the pharmaceutical market more competitive, and would tend to reduce costs for consumers and health care providers.

## **2. Changes in Mandated Disclosures**

Advertising directed at physicians must satisfy the same disclosure requirements applied to DTC advertising. FDA rules appear to assume that advertisements must supply something close to complete prescribing information. Former Commissioner David Kessler, who was also an authority on FDA advertising regulation, argued in 1990 (before being appointed to the FDA) that pharmaceutical advertisements must contain “a balanced account of all clinically relevant information -- the risks and benefits -- that can affect a physician's prescribing decision” (Kessler and Pines 1990). While he was Commissioner, Dr. Kessler endorsed a study that was premised on the assumption that pharmaceutical advertisements should meet the same standards as refereed medical journals (Kessler 1992).

The courts have found that mandated disclosures must be “reasonably related to the State’s interest in preventing deception of consumers.”<sup>16</sup> FDA seems not to have accumulated any evidence for its disclosure standards, however. In a First Amendment challenge to its standards, FDA would probably have considerable difficulty in defending the principle enunciated by Kessler. I therefore recommend that FDA reassess the need for detailed risk-benefit information in all advertising, with the goal of greatly loosening this requirement except for unusual, factually defensible, circumstances.

## **3. Changes in the Regulation of Manufacturer Dissemination of “Off-label” Information to Physicians**

Before Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA), FDA prohibited manufacturers from disseminating any “off-label”

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<sup>16</sup> *Zauderer*, 471 U.S. at 651.

information, i.e., information that does not appear on the FDA-approved labeling. FDA's prohibition included the dissemination of refereed journal articles, textbooks, and practice guidelines from the National Cancer Institute and other authoritative organizations.

FDAMA instructed FDA to permit very limited distribution of off-label information in "enduring materials" such as journal and textbooks (Weeks 1999). The extent to which FDA has met Congressional intentions is currently the subject of litigation between the Washington Legal Foundation and FDA.

It is beyond dispute that much off-label information is extremely valuable, and that off-label prescribing, i.e., prescribing that does not meet all conditions in the FDA-approved label, is common and often medically necessary. A 1997 representative survey of oncologists (Calfee and McGinniss 1997, described in Thakkar 1997) found that off-label prescribing was extremely common in treating cancer, and that oncologists thought that receiving off-label information from manufacturers could be useful. The oncologists also thought they could protect their patients' interests without FDA determining what information they would receive from manufacturers. A 1998 survey of dermatologists in an academic setting (Li, et al. 1998) also found off-label prescribing very common. Other than these two surveys, there appears to be little systematic research on the extent of off-label prescribing, but the fact that it is common, especially when treating children, is undisputed. In 1994, an American Medical Association official estimated that roughly half of all drugs are prescribed for off-label uses, and that the proportion ranged from 60% to 90% in cancer treatment, especially for children (Skolnick 1994).

FDA standards for approving new uses for an existing drug are extremely stringent. Supplement review times during 1989-1994 averaged 28 months, about 4 months longer than review times for entirely new drugs (DiMasi, Brown, and Lasagna 1996). However, physicians are free to prescribe approved drugs for any use they deem medically effective. Hence manufacturers do not submit all valid news uses for FDA approval, even for uses supported by substantial research published in peer-reviewed journals.

The fact that off-label prescribing is often medically necessary is undisputed. In addition to the surveys cited earlier, other sources recognize the essential role of off-label medicine. Authoritative reviews of drug therapy, such as those periodically published in the *New England Journal of Medicine*, typically include off-label uses, often without noting which uses are on or off the label. (A recent example of a drug therapy survey that does emphasize off-label uses is Yanovski and Yanovski 2002.) Textbooks also routinely describe and endorse off-label prescribing (an example being Wolverton's textbook of dermatology, reviewed in Hsu 2002). These sources sometimes note that the FDA-approved label is often very restrictive regarding such details as dosage, timing, and sequence of therapies, far more so than accepted practice (as noted in Li, et al. 1998).

Finally, FDA officials have themselves explicitly noted that many off-label uses are essential, although of course not all off-label uses are beneficial or supported by evidence. Earlier this year, in a *Journal of the American Medical Association* note on the shortage of a drug called IGIV, FDA Commissioner Jane Henney stated, "While there is consensus that efficacy exists for off-label use of IGIV in such diseases as Guillain-Barré syndrome, chronic idiopathic demyelinating polyneuropathy, and myasthenia gravis, many unapproved uses of the product are of unproven efficacy."

FDA seems not to have developed empirical evidence that the dissemination of off-label information is inherently misleading and therefore can be prohibited outright. I think it unlikely that FDA could defend its prohibition of off-label information dissemination against First Amendment challenges. I therefore recommend that FDA apply a rule of reason to the level of evidence required to support dissemination of off-label information.

#### **4. Changes in the Regulation of Manufacturer Dialogues with the Public**

FDA regulations appear to be extraordinarily restrictive in two areas. One is the dissemination of information about products not yet approved for marketing. FDA rules severely restrict manufacturer communications with the investment or medical communities about products in the pre-approval stage. It is far from clear that such

communications are inherently misleading, given the that products in question cannot be prescribed by physicians or used by patients. Nor is it clear why potentially misleading communications cannot be satisfactorily qualified by disclosures about the non-approved status of the products and the lack of FDA endorsement of the results of clinical trials. Again, I recommend that FDA apply an evidence-based rule of reason, the effect of which would presumably be to permit pre-approval communications that are not simply advertising or promotion. In addition, the FDA should reconsider its ban on advertising and promotion of products under review. Pre-approval marketing can serve a useful role by alerting physicians and patients to therapeutic options that may be superior to therapies that could be delayed instead of being used immediately. This kind of information would presumably merit at least the limited Constitutional protections afforded commercial speech.

A second area with inordinate FDA restrictions pertains to the dissemination of information in connection with public debate and attacks. As things stand, manufacturers cannot use advertising to reply to attacks (which themselves often employ advertising) without having FDA treat their replies as commercial communications that require the full apparatus of warnings, etc. Much of this discussion is political or legal, touching on such matters as drug pricing or safety and the manufacturer's responsibility for harm in connection with specific branded drugs. Such speech may well merit more than the limited First Amendment protections accorded purely commercial speech. The current regulatory regime, including the element of leverage discussed above, greatly impedes this kind of speech. I recommend that FDA announce that it will not longer treat such communications as ordinary advertising. That would put an end to the current unfortunate situation in which firms under attack must choose between offending the regulatory staff upon whom their fortunes largely depend, or leaving the public bereft of essential arguments that only the affected firm is able or motivated to make.

## References

- Beales, J. Howard, and Timothy J. Muris (1993) *State and Federal Regulation of National Advertising*, AEI Press.
- Calfee, John E. (2002) "Public Policy Issues in Direct-to-consumer Advertising of Prescription Drugs," working paper, available at [www.aei.brookings.org/publications/related/related\\_02\\_07.pdf](http://www.aei.brookings.org/publications/related/related_02_07.pdf).
- Calfee, John E., and Lamar McGinniss (1997) "A Representative National Survey of Oncologists on Off-Label Prescribing and FDA Policies Toward Information Dissemination," American Enterprise Institute, September 12, 1997.
- Calfee, John E. and Debra Jones Ringold (1994) "The Seventy Percent Majority: Enduring Consumer Beliefs About Advertising," *Journal of Public Policy and Marketing*, Vol. 13, no. 2 (Fall), p. 228-238.
- DiMasi, Joseph A., Jeffrey S. Brown, and Louis Lasagna (1996) "An Analysis of Regulatory Review Times of Supplemental Indications for Already-Approved Drugs: 1989-1994," *30/2 Drug Information Journal* 315-337.
- Federal Trade Commission (1983) "Deception Statement" ("Policy Statement on Deception,"), 45 *Antitrust and Trade Regulation Report* 689 (Oct. 27 1983), appended to *FTC v. Cliffdale Associates, Inc., et al.*, 103 FTC 110, 174-184 (1984.)
- Federal Trade Commission (1984) "Advertising Substantiation Policy Statement," Mimeo, July 27, 1984; reprinted in 47 *Antitrust and Trade Regulation Report* 234-235 (August 2, 1984) and appended to *Thompson Medical Company*, 104 *F.T.C.* 648, 839-942 (1984), *aff'd*, 791 F.2d 189 (D.C. Cir. 1986).
- Ford, Gary T., and Calfee, John E. (1986) "Recent Developments in FTC Policy on Deception" 50 *J. of Marketing* 82-103 (July.)
- Henney, Jane E. (2002) "Continuing Shortage of IGIV," *JAMA*, v. 282 No. 17, p. 1613 (November 3, 1999).
- Hsu, Sylvia (2002) "Review of *Comprehensive Dermatologic Drug Therapy*, edited by Stephen E. Wolverton, *Annals of Dermatology*, v. 138, n. 5 (May).
- Kessler, David A. (1992) "Addressing the Problem of Misleading Advertising (editorial)," 116/33 *Annals of Internal Medicine* 950-951 (June 1).

Kessler, David A., and Wayne L. Pines (1990) "The Federal Regulation of Prescription Drug Advertising and Promotion," 264/18 *Journal of the American Medical Association* 2409-2415 (Nov. 14).

Li, Vincent W., Michael P. Jaffe, William W. Li, and Harley A. Haynes (1998) "Off-Label Dermatologic Therapies: Usage, Risks, and Mechanisms," *Archives of Dermatology*, v. 134, p. 449-1454.

Mamdani, Muhammad M., and Jack V. Tu (2001) "Did the Major Clinical Trials of Statins Affect Prescribing Behavior?", *Canadian Medical Association Journal*, v. 164, n. 12 (June 12).

Morris, Louis, and Lloyd Millstein (1984) "Drug Advertising to Consumers: Effects of Formats for Magazine and Television Advertisements," 39/4 *Food Drug Cosmetic Law J.* 497-503.

Morris, Louis, Michael Ruffner, and Ronald Klimberg (1985) "Warning Disclosures for Prescription Drugs," 25/5 *Journal of Advertising Research* 25-35 (Oct.-Nov.)

Petersen, Melody, and Reed Abelson (2002) "Drug Makers and F.D.A. Fighting Hard Over Quality," *New York Times*, May 17, 2002.

Pines, Wayne L. (1999) "A history and perspective on Direct-to-consumer promotion," 54 *Food and Drug Law Journal* 489-518.

Skolnick, Andrew A. (1994) "Pro-Free Enterprise Group Challenges FDA's Authority to Regulate Drug Company's Speech," 271/5 *J. of the American Medical Association* 332-335 (Feb. 2).

Thakkar, S. (1997) "Oncologists Judge Themselves the Best Judges of Cancer Treatments," 16 *Journal of the National Cancer Institute*, 1188-1189 (August 20, 1997).

*Thompson v. Western States Med. Ctr.*, 122 S. Ct. 1497 (2002)

Yellin, Arthur (1987) "FDA Prescription Drug Enforcement Policies and Techniques," 42 *Food Drug Cosmetic Law J.* 552-558.

Weeks, Elizabeth A. (1999) "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997," *Food and Drug Law Journal*, v. 54, p. 645-666.

Yanovski, Susan Z. and Jack A. Yanovski (2002) "Drug Therapy: Obesity," *New England Journal of Medicine*, v. 346, n. 8, p. 591-602 (February 21, 2002).

## Appendices

Appendix 1: John E. Calfee (2002) "Public Policy Issues in Direct-to-consumer Advertising of Prescription Drugs," forthcoming, *Journal of Public Policy and Marketing*.