THE CRIMINALIZATION OF TRUTHFUL, NON-MISLEADING OFF-LABEL PROMOTION: CONSTITUTIONAL, LEGAL AND POLICY CONCERNS

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Over the last several years, the government has pursued an aggressive campaign against pharmaceutical manufacturers to criminalize truthful, non-misleading speech regarding off-label uses of FDA-approved products. From the perspective of the government, the appeal of this campaign is evident. If truthful, non-misleading promotion of FDA-approved drugs can be refashioned, not as either protected speech or a mere regulatory violation, but rather as *criminal* misconduct, the government may then dispense with the need to prove false or fraudulent representations or other inherently wrongful conduct. The government, in turn, may then proceed, with relative ease, to extract recoveries from pharmaceutical companies in the tens or even hundreds of millions of dollars—all for conduct engaged in prior to the present campaign and without any apparent appreciation in the marketplace that such conduct could give rise to criminal charges.

The lack of understanding in the marketplace is hardly surprising. Throughout the relevant time period, the federal government was itself providing reimbursement for numerous off-label uses of FDA-approved drugs[1] and the FDA was openly and repeatedly acknowledging the value of off-label uses in the practice of medicine.[2] There was no judicial determination that truthful, non-misleading off-label promotion constituted criminal misconduct. And there was no statutory provision in the federal criminal code that provided, clearly and unequivocally, that off-label promotion was forbidden.

Clouded by these considerations, the government's prosecution theory is deeply flawed and gives rise to substantial legal, constitutional and policy concerns. The government nevertheless finds itself in a position to proceed largely unchecked. While it is difficult to conceive of any jury in America convicting an individual of a crime for "pure" off-label speech-related activities, the corporate entities that have been the focus of the government's campaign have no meaningful right to a jury trial and thus no practical ability to challenge in a judicial forum the government's prosecution theory on legal or constitutional grounds.[3] Because in this post-Arthur Andersen era, the corporation cannot risk the potential death knell of a criminal indictment, it cannot afford to test the government's legal theory or to hold the government accountable through the traditional safeguards and protections of a criminal trial.[4]

With the government proceeding apace to pursue and collect substantial recoveries from corporate entities in "settlement" of unproven and untested charges, there is a growing dismay with the current state of affairs in corporate criminal dispute resolution and a corresponding erosion of confidence in the criminal justice system as it applies to corporations. In the off-label arena, with virtually every pharmaceutical company in America under investigation, the frustration is palpable.

Although a far cry from the judicial forum that is contemplated for the resolution of serious legal and constitutional issues, a careful analysis of the infirmities in the government's prosecution theory may provide a starting point in seeking to hold the government accountable and to test the validity of its pronouncement that truthful, non-misleading speech about off-label uses of FDA-approved drugs is criminal. To that end, this article seeks in short compass to highlight the compelling constitutional and policy concerns with the government's prosecution theory, and then turns to the threshold legal issues and focuses in detail on the absence of a viable statutory predicate for the government's position that truthful, non-misleading off-label promotion is a crime.

I. FIRST AMENDMENT CONSIDERATIONS

In *Virginia State Board of Pharmacy*, the Supreme Court first recognized that consumers' interest in receiving accurate commercial information supports an interpretation of the First Amendment that provides constitutional protection for the dissemination of truthful and non-misleading commercial messages:

> So long as we preserve a predominantly free enterprise economy, the allocation of our resources in large measure will be made through numerous private economic decisions. It is a matter of public interest that those decisions, in the aggregate, be intelligent and well informed. To this end, the free flow of commercial information is indispensable.[5]

Because physicians may prescribe FDA-approved drugs off-label, the public—which benefits from the well-informed exercise of medical judgment—has a strong interest in ensuring that physicians have free access to truthful, non-misleading information concerning off-label uses. For this reason, any prohibition on the dissemination of such information is subject to First Amendment scrutiny.

Communications regarding off-label uses of FDA-approved drugs present "complex mixtures of commercial and [pure speech]." [6] When discussed or delivered by a source other than a drug manufacturer, it is beyond dispute that the communication of such information constitutes scientific and academic speech entitled to the highest degree of constitutional protection.[7] Even when delivered by a manufacturer in reference to its own products, however, such communications provide truthful, non-misleading information to physicians and aid them in the exercise of their medical judgment. The First Amendment commands an assumption that physicians, like all people, will make the best decisions "if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them."[8]

A recent United States Supreme Court decision lends strong support to the position that manufacturers' provision of truthful, non-misleading information concerning off-label uses is protected by the First Amendment.[9] In this case, the Court struck down as an impermissible restriction on commercial speech a provision of the Federal Food Drug and Cosmetic Act (the "FDCA") that expressly barred licensed pharmacists from advertising or promoting drug compounding services to consumers. Drug compounding is the process by which a pharmacist or doctor combines, mixes, or alters ingredients—often, FDA-approved drugs—to create a new medication tailored to the needs of an individual patient. The FDA has recognized the value of drug compounding and permits the activity, but has sought to restrict the large-scale manufacture of unapproved drugs.[10] Because banning advertising was not the least restrictive means by which the FDA could ensure that compounding was not occurring on a scale that was undermining the "new drug" approval process, the Court deemed the prohibition on advertising unconstitutional.[11] This holding strongly supports the proposition that, under the commercial speech doctrine, criminal prosecution on the basis of discussions and distribution of truthful, non-misleading information concerning off-label uses is barred by the First Amendment.

II. DUE PROCESS CONSIDERATIONS

Due process requires that "no man shall be held criminally responsible for conduct which he could not reasonably understand to be proscribed."[12] A lack of "fair warning" about a statute's prohibitions offends "a basic principle of due process."[13] Application of the doctrine is "particularly compelling" where the "conduct cannot be deemed improper or immoral."[14]

As then Deputy Attorney General James Comey stated at the 2005 American Bar Association White Collar Crime Conference, in general remarks that are particularly apt with regard to the criminal pursuit of off-label promotion:

> [I]t is inappropriate to use the criminal law to regulate. . . . [W]e should strive as much as we humanly can to understand that our role is to put people in jail for crossing a clearly drawn line—that they saw the line, and they knew the line was there, and they stepped over it. And they are going to get locked up for doing that.[15]

In its present campaign to pursue truthful, non-misleading speech regarding off-label uses of FDA-approved drugs as a criminal matter, the government is eschewing any clearly drawn line and is instead seeking to apply 2006 standards (that the Department of Justice has in no small measure been responsible for developing) to punish conduct that occurred during an earlier period when such speech was viewed not only *not* to be criminal, bur rather to be affirmatively beneficial. Indeed, historically, the FDA itself, in apparent recognition that such speech may be affirmatively good, has sought to regulate off-label discussions between pharmaceutical representatives and physicians only in the context of certain "solicited" communications, leaving the balance of such truthful, non-misleading communications free from any regulatory proscription.

The due process and "fair warning" concerns are exacerbated where, as here, the conduct sought to be punished is not inherently wrongful. Where the conduct cannot be viewed to be intrinsically "improper or immoral,"[16] the imperative of a "clearly drawn line" is all the stronger. The nature of the conduct here in issue, and its beneficial attributes, together with First Amendment considerations and the absence of a direct statutory predicate for a criminal violation (as set forth below), collectively eviscerate any semblance of a clearly drawn line sufficient to justify the imposition of criminal punishment.

III. RELATED POLICY CONCERNS

The constitutional issues, and the wisdom of prosecutorial restraint in this arena, are reinforced by a consideration of the public health and public policy implications of the government's prosecution theory. The prospect of a criminal prosecution in the absence of a "clearly drawn line" alone instills trepidation. When coupled with the speech-related nature of the conduct in issue and the beneficial role that off-label uses play in the practice of medicine, there is a substantial risk that the government's prosecutorial efforts will have the unintended consequence of reducing the crucial, often life-saving, role that off-label treatments play in the practice of medicine.

Specifically, criminal prosecution of free discussion with physicians and dissemination to them of truthful, non-misleading information concerning off-label uses of FDA-approved products raises a serious risk of chilling valuable, protected speech.[17] Drug manufacturers must navigate the FDA's complex regulatory scheme controlling distribution of scientific information concerning off-label uses to physicians. Criminal prosecution of pharmaceutical companies for dissemination of truthful, non-misleading information will likely result in such manufacturers generally avoiding speech on the subject of off-label uses, including speech protected by the First Amendment, and perhaps also speech permitted under the FDA's complex web of regulations.

A criminal prosecution of truthful, non-misleading speech regarding off-label uses could thus have the unintended effect of causing physicians to be less well-informed about the standard of care for the treatment of many diseases. For a disease —cancer, for example—that is in large measure dependent for its treatment on off-label uses, the threat may be of particular significance. The threat is further exacerbated for those types of illness that affect small patient populations, where physicians are less likely to receive information regarding new uses and treatments through the regular mailings and distribution channels of the medical community. Similarly, physicians treating patients in more remote geographic locations may lack access to many of the sources of information available to doctors in urban centers of medical research. Cutting off the flow of scientific information from pharmaceutical representatives in these settings would increase the risk that physicians would not learn as quickly about potential new treatments.

In short, criminal prosecution of drug manufacturers for distribution and discussion of truthful, non-misleading information concerning off-label uses of FDA-approved drugs could have a significant impact on the distribution of scientific information within the medical community. Any significant curtailment of the free flow of truthful, non-misleading information regarding such uses would in turn almost certainly have an adverse impact on the acknowledged beneficial role of off-label uses in the treatment of many diseases, to the detriment of patients and their families.

IV. STATUTORY PREDICATE FOR THE GOVERNMENT'S PROSECUTION THEORY—THE ABSENCE OF A "CLEARLY DRAWN LINE"

The government's theory of prosecution is predicated upon two provisions in the FDCA. Specifically, the government contends that truthful, non-misleading speech regarding off-label uses of FDA-approved drugs is subject to criminal prosecution under the misbranding (no "adequate directions for use") and unapproved new drug provisions of the FDCA.[18]

These statutory provisions are exceptionally technical and precise in their terms and do not neatly fit the government's contention that truthful, non-misleading off-label promotion constitutes a crime. To the contrary, not only is there no "clearly drawn line" by which Congress pronounced truthful, non-misleading off-label promotion to constitute criminal misconduct, but there would appear to be no legally sustainable line at all. As a careful analysis of these provisions makes clear, there are significant gaps in the government's legal theory and no apparent pathway to the claimed criminal prohibition. At bottom, the statutory vehicles upon which the government seeks to predicate a criminal charge do not by their terms proscribe the conduct sought to be criminalized.

A. Adequate Directions for Use

1. The Statute Does Not Apply to Prescription Drugs

A criminal charge that a pharmaceutical company violated the FDCA by failing to provide adequate directions for off-label uses of its prescription FDA-approved products does not lie based on threshold legal grounds. Specifically, the statutory requirement that product labeling include adequate directions for use, 21 U.S.C. § 352(f), applies only to *non-prescription* drugs. Congress so provided; the FDA has so determined; and the courts have upheld the FDA's position as being in accord with congressional intent.

The legislative history of the misbranding provision reveals Congress' purpose that the legislation:

> require the labeling of drugs and devices with information essential to the consumer. The Bill is not intended to restrict in any way the availability of drugs for self-medication. On the contrary, it is intended to make self-medication safer and more effective. For this purpose, provisions are included in this section . . . requiring that labels bear adequate directions for use . . . .[19]

The FDA's own regulations provide that "adequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended."[20] The courts that have considered the question are in accord.[21] Accordingly, the statutory vehicle the government proposes to use to charge drug manufacturers criminally for off-label promotion of their prescription drug products has been expressly determined not to cover such drugs, but rather to apply only to non-prescription, over-the-counter drugs to ensure that the consumer has adequate directions to self-administer such drugs in a safe and effective manner.

2. The Criminal Charge Cannot Be Predicated on FDA Regulations Where Congressional Authorization Is Lacking

Since the statutory provision on adequate directions for use does not itself apply to prescription drugs, a criminal charge against a manufacturing company for failing to provide adequate directions for use for its prescription drug products could be predicated, if at all, only upon an alleged violation of a regulation promulgated by the FDA that purports, in convoluted fashion, to create and then set the terms of an exemption to the "adequate directions for use" requirement for prescription drugs.[22] An agency is permitted to define criminal conduct by regulation, however, *only* where Congress has expressly made violation of the regulations a criminal offense. As the United States Supreme Court has observed, an agency may "define[] by regulation what conduct will be criminal, so long as Congress makes the violation of regulations a criminal offense and fixes the punishment."[23] Nowhere in the FDCA does Congress state that violations of regulations promulgated pursuant to the Act are criminal offenses. Therefore, while 21 C.F.R. § 201.100, if valid, may support civil remedies, it cannot provide the basis for a criminal charge.

3. The Regulation Is in Any Event Inconsistent with the Statute and Therefore Invalid as a Basis upon Which to Predicate a Criminal Charge

The regulation is squarely at odds with the statute. Specifically, while the statute allows adequate directions in the "labeling," which can include scientific articles and other written material "accompanying" the product,[24] the regulation purports to limit the location of the directions to material on or within the package.[25] As such, conduct that would be permissible under the statute is criminal under the regulation. This critical narrowing in the regulatory provision, which on its face is inconsistent with the statute, further demonstrates that it is the regulation, not the statute, that imposes the purported obligation that the pharmaceutical company would be charged with violating. Violation of an FDA regulation cannot properly form the basis for a criminal charge, as noted above, and the principle holds particularly true where, as here, the regulation is inconsistent with the statute.[26]

4. Summary of Flaws in Government's "No Adequate Directions for Use" Misbranding Theory

In short, the government's prosecution theory—that pharmaceutical companies are criminally liable for misbranding of their FDA-approved prescription drug products where the companies fail to provide "adequate directions for use" for these products—is flawed on three distinct grounds. First, the "no adequate directions for use" misbranding statute does not apply

to prescription drugs, as the legislative history of the FDCA and congressional intent make clear (as confirmed and reinforced by the relevant case law and the FDA's own interpretation of the statute). Second, the regulatory foundation upon which the government's prosecution theory is predicated cannot sustain a criminal charge, as the FDA promulgated the regulation not only without express congressional direction, but also—by reaching to cover prescription drugs—in a manner that extended beyond the four corners of the field covered by the statute. Finally, and confirming the invalidity of the regulation as a predicate for a criminal charge, the regulation purports to criminalize conduct that Congress determined to be—and expressly left—in the wide zone of permissible behavior. Moreover, to the extent Congress required "adequate directions for use" (for non-prescription products), Congress did not limit the location of such directions to "the package" itself, as the regulation improperly purports to do.

While the FDA has substantial authority to promulgate regulations pursuant to the FDCA, it does not legally or constitutionally have the power to define by regulation what conduct is criminal, or to promulgate regulations that either reach beyond the field covered by the statute or are inconsistent with that field as demarcated by Congress. The government's theory of prosecution here violates all three principles.

B. Unapproved New Drug

Section 301(d) of the FDCA, 21 U.S.C. § 331(d), prohibits the introduction or delivery into interstate commerce of any article in violation of section 505 of the FDCA, 21 U.S.C. § 355. Section 505(a), in turn, prohibits any person from introducing or delivering for introduction into interstate commerce any "new drug" unless the drug has been approved by the FDA.[27] In order to prove an offense under the "new drug" provisions based on distribution of truthful, non-misleading information concerning off-label uses for approved drugs, the government would have to show:

- that the pharmaceutical company distributed printed labeling that accompanied its drugs;
- that the labeling recommended or suggested that the drugs be prescribed for an off-label use;
- that the labeling thereby made the drug an unapproved "new drug" not generally recognized, among qualified experts, as safe and effective for the off-label use; and
- that the drug was shipped in interstate commerce.

Under the statutory definition of a "new drug," only off-label uses promoted through "labeling" are relevant. Pursuant to 21 U.S.C. § 321(p), "the term 'new drug' means . . . any drug . . . not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended or suggested *in the labeling* thereof . . . ."[28] The term "labeling," as used in the statute, is a term of art. Specifically, the statute defines "labeling" to include "all labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[29] As such, the statutory term "labeling" is limited to physical labels and other "written, printed or graphic matter" accompanying the product. The law is well-settled that "labeling" has this defined meaning.[30]

A charge based on the new drug provisions must be consistent with the statutory definition of a "new drug," which, in turn, relies exclusively on labeling. The cases on intended use that the government has in the past relied upon in connection with its "unapproved new drug" theory are inapposite. While those cases permit reliance on all statements and other representations to show the intended use of a product, they all involve the issue of whether an article is a "drug," and not whether the article is a "new drug" for new drug approval purposes.[31] The distinction is critical. Moreover, in those cases where a violation of the new drug provisions has been found to have occurred, all involved as a factual predicate written "labeling" that contained statements "prescrib[ing], recommend[ing], or suggest[ing]" the use.[32] Accordingly, where the off-label promotion in issue involves communications and discussions between pharmaceutical representatives and physicians and does not involve the distribution of any "labels" or "other written, printed or graphic matter," that "prescribed, recommended, or suggested" off-label uses of the drug in issue, there can be no violation of the new drug approval provisions.

Finally, even where a pharmaceutical company has distributed printed labeling prescribing, recommending or suggesting an FDA-approved product for one or more off-label uses, there is no violation of the new drug approval provisions where the drug in question can be shown to be "generally recognized as safe and effective" for the prescribed off-label use. While the FDA is responsible for determining whether a product is "safe and effective," the law is clear that various sources, including published scientific literature and clinical experience, may be used to demonstrate that a drug is "generally recognized" to be safe and effective.[33]

* * *

In short, and as the foregoing analysis demonstrates, the statutory provisions in the FDCA upon which the government seeks to rely in its pursuit of criminal charges for truthful, non-misleading off-label promotion do not reach the conduct that the government seeks to define

as criminal. The statutory provisions were enacted decades ago, with other purposes in mind, and long before the government developed, early in the 21st Century, its novel prosecution theory. These statutory provisions cannot, at this late stage, fairly be re-construed to extend to truthful, non-misleading off-label promotion of FDA-approved prescription drug products.

V. CONCLUSION

Analysis of the government's prosecutorial efforts to criminalize truthful, non-misleading off-label promotion of FDA-approved products should begin and end with the serious question of whether such off-label promotion is even a crime. There has been no judicial determination, ever, that truthful, non-misleading off-label promotion constitutes criminal misconduct. There is no statutory provision that directly provides that one "shall not off-label promote." Moreover, the statutory provisions relied upon by the government do not easily fit the government's prosecution theory. And the very nature of the asserted prohibition raises substantial questions regarding whether Congress plausibly could have intended to prohibit the conduct in the manner asserted by the government; after all, such a prohibition would represent an anomaly in the federal criminal code, as there is no other provision therein that singles out a particular class of speakers, prohibits only them from speaking about a lawful activity, and threatens to punish them criminally for such speech-related activities.

Even assuming, however, that the government could somehow muster a showing that truthful, non-misleading off-label promotion is criminally proscribed, there are further serious concerns regarding the government's prosecutorial effort. There are substantial constitutional questions. There are important issues regarding the inherent unfairness of imposing punishment for conduct that is not only *not* inherently wrongful, but also arguably beneficial, in the absence of a clearly drawn line. There is genuine risk, from a public health and policy perspective, that prosecutions focused on truthful, non-misleading speech about off-label uses will chill valuable, protected speech and thereby have an adverse impact on the acknowledged beneficial role of off-label uses in the treatment of various diseases, to the direct detriment of patients and their families.

For all of these reasons, the government should exercise restraint in the off-label arena. At a minimum, and before the government proceeds further with its efforts to extract tens or even hundreds of millions of dollars from pharmaceutical companies on the basis of such a novel and troubled theory of criminal liability, it should put the strength of its convictions on the line in a court of law.

ENDNOTES

1. Pursuant to federal and state reimbursement regulations, and by virtue of their inclusion in one or more of the recognized medical compendia or through studies published in peer-reviewed medical literature, many off-label uses are reimbursable by Medicare or Medicaid and under state insurance laws. See 42 U.S.C. § 1395x(t)(2); Medicare Carriers Manual 2049.4C.

2. The FDA has repeatedly taken the position that off-label uses of approved drugs are proper. It affirmatively acknowledged their value over twenty years ago in a Drug Bulletin informing the medical community that "once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling." See 12 FDA Drug Bulletin 4-5 (1982) (cited in 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994)). It also noted that off-label uses "may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature." See id. The policy set forth in this bulletin has been reaffirmed by the FDA on multiple occasions. See, e.g., 52 Fed. Reg. 8798, 8803 (Mar. 19, 1987); 48 Fed. Reg. 26720, 26733 (June 9, 1983); 40 Fed. Reg. 15392, 15393-94 (Apr. 7, 1975); 37 Fed. Reg. 16503, 16503-16504 (Aug. 15, 1972). In addition, in the foreword of the Physician's Desk Reference, one of the primary sources from which physicians obtain information about approved uses for drugs, see Fran Kritz, FDA Seeks to Add Drugs' New Uses to Labels, Wash. Post, Health Section, Mar. 29, 1994, the FDA observes that "accepted medical practice includes drug use that is not reflected in approved drug labeling." See Legal considerations in off-label medication prescribing, 162(15) Archives of Internal Medicine 1777 (August 2002).

   The FDA has also acknowledged before Congress that off-label use is prevalent in and central to the practice of certain medical specialties. Speaking before the House Committee on Government Reform and Oversight, the Deputy Commissioner for Operations of the FDA testified that "off label use is very high for oncology drugs." He further stated that:

   > [o]ff label uses, particularly for oncology, rare diseases, and pediatrics, can be of great value ... It is inevitable that there will be preliminary support for off label uses before definitive information becomes available. Physicians confronted with patient needs may choose to act on such data, especially where there are no good alternatives.

   Michael Friedman, Deputy Comm'r for Operations, FDA, Testimony on Supplemental Indications for Approved Prescription Drugs Before the House Committee on Government

Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations (Sept. 12, 1996), available at http://www.hhs.gov/asl/testify/t960912a.html.

In addition, the FDA's Deputy Commissioner for Policy testified, "FDA knows that there are important off label uses of approved drugs. In this context, it is important that physicians have access to accurate information about drugs." See More Information for Better Patient Care: Hearing on S. 1477 Before the S. Comm. on Labor and Human Resources, 104th Cong. 81 (1996) (statement of William B. Schultz, Deputy Comm'r for Policy, FDA). Similarly, the FDA's Associate Commissioner for Health Affairs declared that the "principle for the FDA is that the very latest information that can be of value to physicians, pharmacists, and patients must be made available as soon as possible. Frequently, unlabeled use information is extremely important." See Stuart J. Nightingale, Associate Commissioner for Health Affairs, Unlabeled Uses of Approved Drugs, 26 Drug Info. J. 141, 145 (1992).

These statements collectively reflect an acknowledgement of the particular value of off-label uses – and information concerning these uses – in the practice of medicine.

3. See Joan McPhee, Corporate Criminal Liability and Punishment in the 21st Century: Departures from Constitutional and Criminal Norms and Anomalies in Practice, 2005 ABA White Collar Crime Conference, at 8-11 (Mar. 2005) (and authorities cited therein), available at http://www.ropesgray.com/files/tbl_s20News/FileUpload116/878/Article_2005_Corporate%20Criminal%20Liability_McPhee.pdf.

4. See id. at 4-8 (and authorities cited therein).

5. Virginia St. Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 765 (1976).

6. Bolger v. Youngs Drug Prods., 463 U.S. 60, 81 (1983) (Stevens, J., concurring).

7. See Keyishian v. Bd. of Regents, 385 U.S. 589, 603 (1967).

8. Virginia St. Bd. of Pharmacy, 425 U.S. at 770.

9. See Thompson v. Western States Med. Ctr., 535 U.S. 357 (2002).

10. See id. at 371.

11. See id. at 373.

12. Bouie v. City of Columbia, 378 U.S. 347, 351 (2002) (quoting United States v. Harriss, 347 U.S. 612, 617 (1954)).

13. Grayned v. City of Rockford, 408 U.S. 104, 108 (1972).

14. Bouie, 378 U.S. at 362.

15. Remarks of Deputy Attorney General James B. Comey, Esq., at ABA White Collar Crime Conference (Mar. 2005), available at http://ww.abanet.org/crimjust/wcc/ABA%202005%20white%20white%20collar%20crime%20conference.htm.

16. Bouie, 378 U.S. at 362.

17. In the context of public discourse, false or misleading speech is protected by the First Amendment because its restriction would lead speakers to curb their speech in order to avoid potential liability – that is, speech would be "chilled." See New York Times Co. v. Sullivan, 376 U.S. 254, 300-301 (1964). By contrast, regulation of false or misleading commercial speech is permissible because commercial speech is thought less susceptible to chilling for two reasons: its truth is more easily verifiable by the speaker, and the speaker is motivated by profit. See Virginia St. Bd. of Pharmacy, 425 U.S. at 771 n. 24. Nevertheless, the Supreme Court has never stated that commercial speech cannot be chilled. Indeed, the threat that protected speech will be chilled is much greater where, as here, the regulation at issue reaches beyond false or misleading speech. Moreover, the chilling effect of a regulation can have as much to do with the potential penalty as the motivation for the speech: "A five dollar fine in a political speech case is probably less of a deterrent than a jail sentence – or disbarment – in a commercial speech case." Daniel A. Farber, Commercial Speech and First Amendment Theory, 74 Nw. U. L. Rev. 372, 386 (1979). See also Robert Post, The Constitutional Status of Commercial Speech, 48 UCLA L. Rev. 1, 31-32 (2000). Thus, even a disclosure requirement – which is inherently less restrictive of speech than a prohibition – may "offend the First Amendment by chilling protected commercial speech" where it is "unjustified or unduly burdensome." Zauderer v. Office of Disciplinary Counsel of the Supreme Court of Ohio, 471 U.S. 626, 651 (1985).

18. See 21 U.S.C. § 331(a), which prohibits the introduction into interstate commerce of drugs in violation of the misbranding provisions of the FDCA that require "adequate directions for use" (21 U.S.C. § 352 (f)); see also 21 U.S.C. § 331(d), which prohibits the introduction into interstate

commerce of articles in violation of the new drug approval provisions of the FDCA (21 U.S.C. § 355).

19. See H.R. Rep. No. 75-2139, at 8 (1938), reprinted in VI Legislative History of the Federal Food, Drug, and Cosmetic Act and its amendments 299, 307 (1979).

20. See 21 C.F.R. § 201.5.

21. See, e.g., United States v. Guardian Chemical Corp., 410 F.2d 157, 160 (2d Cir. 1969) ("if the drug is not one which for safety's sake should be administered only by a physician, its 'labeling' must bear adequate directions for its use"); United States v. Articles of Drug, 625 F.2d 665, 673 (5th Cir. 1980) ("[W]e hold that a drug's labeling must contain adequate directions for a consumer to engage in self-medication.").

22. See 21 C.F.R. § 201.100. Specifically, the FDCA allows the FDA by regulation to exempt products from the adequate directions for use requirement where it is "not necessary for the protection of the public health." 21 U.S.C. § 352(f). Having interpreted the statutory "adequate directions for use" provision, consistent with congressional intent, to apply only to nonprescription drugs, see 21 C.F.R. § 201.5, the FDA then, inexplicably, purported to create a conditional "exemption" for prescription drugs from the statutory requirement, 21 C.F.R. § 201.100, that by its terms requires compliance with the conditions of the exemption to avoid a "no adequate directions for use" misbranding violation. Through this structure, which is entirely a creature of FDA regulations, the only way in which manufacturers of prescription drugs can comply with the requirement for adequate directions for use is to comply with the terms of the exemption. One condition for the exemption to apply is that the labeling "on or within the package from which the drug is to be dispensed" must bear adequate directions for use and adequate warnings for all purposes for which the drug is advertised or represented. Id. Thus, the FDA has sought to create by regulation a separate and distinct prescription drug "no adequate directions for use" prohibition that is expressly absent from the statute.

23. Loving v. United States, 517 U.S. 748, 768 (1996); see also United States v. Grimaud, 220 U.S. 506, 521 (1911) (upholding conviction for violation of regulations promulgated pursuant to Forest Reserve Acts because "[t]he same act makes it an offense to violate those regulations"); Groves v. Modified Retirement Plan, 803 F.2d 109, 117 (3d Cir. 1986) ("Congress will be understood to have authorized agencies to decide what conduct should be penalized only if the legislature has expressly granted that power"); United States v. Seelig, 622 F.2d 207, 210 (6th Cir. 1980) ("[A] person may be held criminally liable for the violation of a regulation, but only if

the statute which authorizes the promulgation of the regulations makes the violation of the regulations a crime.").

24. The term "accompanying" has been construed broadly by the Supreme Court and includes labels or other "written, printed, or graphic matter" whenever it "supplements or explains [another article or thing] . . . . No physical attachment [of] one to the other is necessary." Kordel v. United States, 335 U.S. 345, 348-350 (1948). The Court reached its conclusion based on the second clause of the definition, which extends "labeling" to materials "accompanying such article." See id. This clause has "no specific reference to packages, containers or their contents as did a predecessor statute. See id. (citing Seven Cases v. United States, 239 U.S. 510, 513, 515 (1916)). Relying in part on this shift in the legislative history, the Court held more generally that "[t]he textual structure of the [FDCA] is not agreeable to [a construction limiting labeling to packages or containers]," and that the broader reading of "labeling" and "accompanying" is "plainly embraced within the language of the statute." Kordel , 335 U.S. at 349 (citing United States v. Resnick, 299 U.S. 207, 209-10 (1936) and Kraus & Bros. v. United States, 327 U.S. 614, 621-22 (1946)).

25. See 21 C.F.R. § 201.100(c).

26. See Illinois by Ill. Dep't of Public Aid v. U.S. Dep't of Health, 772 F.2d 329, 334 (7th Cir.1985) ("It is clear that a regulation which is inconsistent with the statute under which it is promulgated is invalid.").

27. The FDCA defines a "new drug" as: "(1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, . . . or (2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." 21 U.S.C. § 321(p).

28. 21 U.S.C. § 321(p) (emphasis added).

29. 21 U.S.C. § 321(m).

30. See, e.g., United States v. 24 Bottles, 338 F.2d 157, 158 (2d Cir. 1964); Alberty Food Products v. United States, 185 F.2d 321, 325 (9th Cir. 1950).

31. United States v. Articles of Drug, 239 F. Supp. 465 (D.N.J. 1965) (oral representations made the vitamins drugs; charge was failure to provide adequate directions for use, not violation of the new drug provisions); see also cases cited, supra, at p. 2.

32. United States v. Hiland, 909 F. 2d 1114, 1121 (8th Cir. 1990) (claims included in the package insert and brochure); United States v. Kasz Enters., Inc., 855 F. Supp. 534, adopting magistrate's report and recommendation, 1994 U.S. Dist. LEXIS 8597, *22-*31 (D.R.I. 1994) (product considered new drug based on "labeling and promotional materials); Nutrilab, Inc. v. Schweiker, 547 F. Supp. 880, 883 (N.D. Ill. 1982) (claims included in "promotional materials and labeling").

33. See , e.g., Premo Pharmaceutical Labs., Inc. v. United States, 629 F.2d 795, 803-04 (2d Cir. 1980).