



FDA Guidance Regarding the Promotion of Off-Label Uses of Drugs: Legal Issues

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Summary

New drugs may not be introduced or marketed without the approval of the Food and Drug Administration (FDA). When a person submits a drug application to the FDA for approval, the application includes samples of the proposed labeling. The FDA may refuse to approve an application if the drug is not safe or effective for the specific uses that are reflected in its labeling. An unapproved new use of a drug, also known as an off-label use, is a use not mentioned in the drug's approved labeling. Although a physician may prescribe a drug for off-label uses, a pharmaceutical manufacturer may not market or promote uses of a drug other than those on the label—those uses approved by the FDA in the application.

In January 2009, the FDA issued a guidance document on the dissemination of medical information regarding off-label uses of drugs. The guidance seemingly creates a safe harbor for dissemination of information on off-label uses of FDA-approved drugs and medical devices. However, the agency's guidance statement does not have the force or effect of law, and the FDA still retains its legal authority under the Federal Food, Drug, and Cosmetic Act (FFDCA) and FDA regulations to determine when promotion of an unapproved new use has occurred or when a product is misbranded. Additionally, the guidance does not affect the legal authority, enforcement powers, or other capabilities of outside entities that have been involved in prosecuting False Claims Act (FCA) cases related to off-label marketing and the submission of false claims for reimbursement from the U.S. government.

First, this report outlines the relevant provisions of the FFDCA and related regulations that have been used to address misbranding violations of the act that relate to pharmaceutical manufacturers' promotion of off-label use. Second, the report summarizes the FDA's previous off-label marketing provisions under the FDA Modernization Act of 1997 (FDAMA), which are no longer in effect. Third, the report details the January 2009 guidance document and its similarities to and differences from the FDAMA provisions. Fourth, the report outlines First Amendment challenges to FDAMA and older FDA guidance documents addressing off-label promotion. Fifth, the report discusses the nature of guidance documents, in contrast to rules promulgated under the Administrative Procedure Act (APA), as well as administrative law issues associated with the FDA's issuance of the guidance. Sixth, the report provides an overview of the FCA and related *qui tam* cases that addressed off-label marketing practices of pharmaceutical companies. Finally, the report analyzes the interaction of the new guidance document and the FCA.

Contents

FDA Laws, Regulations, and Guidance Documents on Off-Label Use.....	1
Relevant Provisions of the Federal Food, Drug, and Cosmetic Act and Related Regulations.....	1
The FDA Modernization Act’s Off-Label Marketing Provisions	3
Legislative History	5
The FDA’s January 2009 Guidance	6
Administrative Law Issues.....	8
Rules and Guidance Documents.....	8
Is the Guidance a Substantive Rule Subject to a Notice-and-Comment Rulemaking?	9
Does the FDA Have the Authority to Issue the Guidance?	10
First Amendment Challenges.....	12
False Claims Act Issues	16
The False Claims Act.....	16
False Claims Act Cases Involving Off-Label Promotion	16
Interaction of the FDA Guidance with the False Claims Act	19

Contacts

Author Contact Information.....	22
Acknowledgments	22

On January 13, 2009, the Food and Drug Administration (FDA) issued a notice in the *Federal Register* regarding the availability of its guidance for industry on the distribution of medical journal articles and scientific publications regarding unapproved new uses (also known as off-label uses) of approved drugs.¹ The guidance seemingly creates a safe harbor for dissemination of information on off-label uses of FDA-approved drugs.² The FDA's guidance contains provisions similar to, and potentially more expansive than, the provisions on dissemination of information on off-label uses in § 401 of the FDA Modernization Act of 1997 (FDAMA), which expired in 2006. No similar provision was included in the most recent piece of major FDA legislation, the FDA Amendments Act of 2007 (FDAAA).

First, this report outlines the relevant provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA) and related regulations that have been used to address misbranding violations of the act that relate to pharmaceutical manufacturers' promotion of off-label use. Second, the report summarizes the FDA's previous off-label marketing provisions under FDAMA § 401, which are no longer in effect. Third, the report details the January 2009 guidance document and its similarities to and differences from the FDAMA provisions. Fourth, the report outlines First Amendment challenges to FDAMA and older FDA guidance documents addressing off-label promotion.³ Fifth, the report discusses the nature of guidance documents, in contrast to rules promulgated under the Administrative Procedure Act (APA), as well as administrative law issues associated with the FDA's issuance of the guidance. Sixth, the report provides an overview of the False Claims Act (FCA) and related *qui tam*⁴ cases that addressed off-label marketing practices of pharmaceutical companies. Finally, the report analyzes the interaction of the new guidance document and the FCA.

FDA Laws, Regulations, and Guidance Documents on Off-Label Use

Relevant Provisions of the Federal Food, Drug, and Cosmetic Act and Related Regulations

Until the FDA has approved a new drug pursuant to either a new drug application, an abbreviated new drug application, or an investigational new drug submission, the new drug may not be "introduc[ed] or deliver[ed] for introduction into interstate commerce."⁵ When a person submits a new drug application to the FDA for approval, the application includes samples of the proposed

¹ Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694 (Jan. 13, 2009) [hereinafter Guidance Notice].

² While the guidance applies to FDA-approved drugs and medical devices, this report focuses on drugs, as it appears the majority of False Claims Act suits relate to the unlawful promotion of off-label use of prescription drugs.

³ See FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, Guidance, <http://www.fda.gov/oc/op/goodreprint.html> [hereinafter Guidance].

⁴ "Qui tam is short for 'qui tam pro domino rege quam pro se ipso in hac parte sequitur,' which means 'who pursues this action on our Lord the King's behalf as well as his own.'" *Rockwell Int'l Corp. v. United States*, 549 U.S. 457 n.2 (2007).

⁵ 21 U.S.C. § 355(a).

labeling for the drug.⁶ The FDA may refuse to approve a new drug application if the HHS Secretary finds, among other possibilities, that it is not safe or effective “for use under the conditions prescribed, recommended, or suggested in the proposed labeling.”⁷ In other words, the FDA approves drugs for specific uses that are reflected in their labeling. An unapproved use of a drug, also known as an off-label use, has been defined as a “use for indication, dosage form, dose regimen, population [i.e., the drug is approved for adults but not children] or other use parameter not mentioned in the approved labeling.”⁸ While a physician may prescribe a drug for off-label uses,⁹ a pharmaceutical manufacturer may not market or promote a drug for uses other than those on the label—those uses approved by the FDA in a drug application.¹⁰ Off-label uses have been estimated to account for 21% of all prescription drug use.¹¹

Manufacturer marketing and promotion of off-label uses is linked to the FDCA’s prohibition against misbranding.¹² The concept of misbranding is one of the basic components of the FDCA, and persons who violate the act’s prohibitions are subject to criminal and civil penalties, as well as injunctions and seizures of the misbranded product. A drug or device shall be deemed to be misbranded if, among other possibilities, the labeling is false or misleading¹³ or if its labeling does not bear “adequate directions for use.”¹⁴

The phrase “adequate directions for use” means “directions under which the layman can use a drug safely and for the purposes for which it is intended.”¹⁵ An “intended use,” in turn, “refer[s] to the objective intent of the persons legally responsible for the labeling of drugs,” such as the drug’s manufacturer, and that person’s objective intent may be shown by “labeling claims,

⁶ 21 U.S.C. § 355(b)(1)(F).

⁷ 21 U.S.C. § 355(d).

⁸ FDA, Janet Woodcock, A Shift in the Regulatory Approach (June 1997), slide 3, <http://www.fda.gov/cder/present/diamontreal/regappr/sld001.htm>.

⁹ “Allowing physicians to prescribe drugs for such ‘off-label’ usage ‘is an accepted and necessary corollary of the FDA’s mission to regulate [pharmaceuticals] without directly interfering with the practice of medicine.” United States ex rel. Franklin v. Warner-Lambert Co., 147 F. Supp. 2d 39 (D. Mass. 2001) (quoting Buckman Co. v. Plaintiffs’ Legal Comm., 531 U.S. 341 (2001)). See also Medicare Part B, which provides coverage for certain off-label uses of approved drugs. Section 1861(t) of The Social Security Act, 42 U.S.C. § 1395x(t); FDA, *supra* note 8, at slides 4-5.

¹⁰ See 21 U.S.C. § 331(a), (d); Washington Legal Foundation v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000); Franklin, 147 F. Supp. 2d at 44.

¹¹ Anna Wilde Mathews and Avery Johnson, *Boost for Off-Label Drug Use—FDA Would Let Firms Keep Doctors Informed on Unapproved Methods*, Wall St. J., Feb. 16, 2008, at A3.

¹² See 21 U.S.C. § 331(a) (prohibiting “[t]he introduction or delivery for introduction into interstate commerce of any ... drug [or] device . . . that is adulterated or misbranded”); 21 U.S.C. § 331(d) (prohibiting “[t]he introduction or delivery for introduction into interstate commerce of any article in violation of section ... 505 [approval of new drug applications]”); 21 U.S.C. §§ 331(c), (k) (prohibiting the receipt and delivery or proffered delivery of misbranded drugs and devices as well as “the doing of any other act while such [drug or device] is held for sale ... after shipment in interstate commerce [that] results in such article being adulterated or misbranded”).

¹³ 21 U.S.C. § 352(a).

¹⁴ 21 U.S.C. § 352(f)(1).

¹⁵ 21 C.F.R. § 201.5. There are exemptions from “adequate directions for use,” but the exemption for prescription drugs still requires the drug’s labeling to “bear[] adequate information for its use, including indications, effects ... and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and ... the labeling bearing such information is the labeling authorized by the approved new drug application.” 21 C.F.R. § 201.100(c). The labeling in such a case must contain “adequate information for such use ... [in] the same language and emphasis as labeling approved and permitted, under the provisions of section 505 [new drug applications], and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling.” 21 C.F.R. § 201.100(d).

advertising matter, or oral or written statements by such persons or their representatives.”¹⁶ Intended use may also “be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.”¹⁷ Manufacturers are “required to provide adequate labeling for” off-label uses of a drug that the “manufacturer knows, or has knowledge of facts that would give him notice that [the] drug ... is to be used for conditions, purposes, or uses other than the ones for which he offers it.”¹⁸ It appears then that, if a drug manufacturer promotes an intended use that is an off-label use, the drug’s label will not bear adequate directions for use and will thus be a misbranded drug.¹⁹ A drug manufacturer would therefore be required to submit a supplemental new drug application for that off-label use and accompanying label or dosage changes.²⁰

The FDCA defines labeling as “all labels and other written, printed or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”²¹ Labeling includes brochures, motion picture films, and literature, as well as

reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ‘Physician’s Desk Reference’) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor.²²

It appears that a reprint of an article published in a medical journal that is presented to a doctor by a pharmaceutical representative could fall within the FDCA’s labeling provisions and accompanying regulations.

The FDA Modernization Act’s Off-Label Marketing Provisions

Before Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997, the FDA had issued several guidance documents regarding off-label promotion in 1996 regarding the industry’s dissemination of reprints and reference texts.²³ FDAMA § 401 superseded those guidance documents and generally enabled manufacturers to disseminate information about new, or off-label, uses under specified conditions, but only if the manufacturer submitted a supplemental new drug application for the off-label use.²⁴ FDAMA § 401 expired on

¹⁶ 21 C.F.R. § 201.128.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ Based on 21 C.F.R. § 201.128, it appears that if the manufacturer learns that the drug is being used off-label, that the drug could also be misbranded. However, it does not appear that courts have found “that a product ‘is intended for use’ or ‘intended to affect’ within the meaning of the [FDCA] absent manufacturer claims as to that product’s use.” *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 147 (May 2, 2002) (quoting *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998), *aff’d*, 529 U.S. 120 (2000)).

²⁰ *See* 21 C.F.R. § 314.70.

²¹ 21 U.S.C. § 321(m).

²² 21 C.F.R. § 202.1(l)(2).

²³ 61 Fed. Reg. 52800 (Oct. 8, 1996). After the passage of FDAMA, the FDA issued a 1997 guidance on industry-supported scientific and continuing medical education activities that is still in effect. 62 Fed. Reg. 64073 (Dec. 3, 1997).

²⁴ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-3(a)). FDAMA also addressed information regarding off-label uses of devices, which could be disseminated if the product was in commercial distribution and complied with specified (continued...)

September 30, 2006.²⁵ Other than the FDA's 2009 guidance document, it does not appear that the FDA currently has another statute, rule, or policy in effect that explicitly addresses the dissemination of reprints or reference texts with regard to promoting an off-label use.²⁶ This section details the FDAMA provisions, which are similar, in parts, to those in the recent FDA guidance and which provide a basis for understanding current discussions of the FDA's January 2009 guidance.

As emphasized in a *Federal Register* notice post-FDAMA, § 401 created a safe harbor. As long as information dissemination on off-label uses adhered to FDAMA, it was not to be construed as evidence of a new intended use of a drug that differed from the intended use described in its official labeling.²⁷ Nor was it to be considered labeling, adulteration, or misbranding under the FDCA.²⁸ To disseminate information, the manufacturer was required to submit to the Secretary a copy of the information 60 days before distribution, including clinical trials and clinical experience about the safety and effectiveness of the unapproved use, and to comply with the requirements for filing a supplemental new drug application.²⁹

Manufacturers were required to include a prominent statement showing the following, if applicable: that the information concerned an unapproved use of a drug; that the disseminated information was being paid for by the manufacturer; the names of any authors with financial ties with the manufacturer; the official labeling for the drug; a statement that there were other approved products or treatments for the use for which the information was being disseminated; and the identification of all persons who funded any study about the off-label new use.³⁰ Manufacturers were also required to include a bibliography of published articles about the unapproved use from scientific or medical journals.³¹

If the Secretary determined, after providing notice and an opportunity for a meeting, that the off-label use information failed to provide objective and balanced information, the Secretary could have required the dissemination of additional information, along with a statement of the Secretary about the safety and effectiveness of the drug's unapproved use.³²

(...continued)

classification and premarket approval regulations.

²⁵ According to a letter from House Oversight and Government Reform Committee Chairman Henry Waxman to FDA Commissioner Andrew von Eschenbach, "There was no effort to renew section 401 when Congress passed the FDA Amendments Act of 2007." Letter from Henry A. Waxman, Chairman, House Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, FDA, Nov. 30, 2007, at 5, <http://oversight.house.gov/documents/20071130102744.pdf>. FDAMA § 401(f) required studies by the General Accounting Office (now the Government Accountability Office, GAO) and the Institute of Medicine to examine, among other things, the quality and usefulness of information disseminated and whether the § 401 termination date should be extended. According to an individual at GAO who was not involved in the discussions at that time, neither study was conducted. Telephone conversation with GAO employee, Mar. 12, 2008.

²⁶ *See id.* (noting that 21 C.F.R. Part 99 and the FDAMA § 401 implementing regulations are now invalid); *see also* Letter from Henry A. Waxman, Chairman, House Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, FDA, Jan. 22, 2008, at 2 n. 3, <http://oversight.house.gov/documents/20080122141935.pdf>.

²⁷ 63 Fed. Reg. 31143, 31144 (June 8, 1998).

²⁸ *Id.* at 31144.

²⁹ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(b)(4)-(5)).

³⁰ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(b)(6)(A)).

³¹ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(b)(6)(B)).

³² P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(c)).

Manufacturers were allowed to disseminate information about an unapproved new use only if the information was in the form of an unabridged reprint or copy of an article peer reviewed by experts. The unabridged article was required to originate from a medical journal or a reference publication, describe a scientifically sound clinical investigation, and not be false or misleading.

In addition, to disseminate off-label use information, manufacturers were required to prepare and submit biannually to the Secretary a list of articles and reference publications about their drug's unapproved uses that were disseminated for the six-month period prior to the submission of the list. Manufacturers were also required to submit lists that identified the categories of providers that received that material for the same time period.

If the Secretary determined that the unapproved use may not have been effective or may have presented a significant risk to the public health, the Secretary could have ordered corrective action, including the cessation of dissemination of the information. In the event that the Secretary required corrective action to be taken, manufacturers had to keep records regarding the dissemination of off-label information that could be used in such situations. Manufacturers were also responsible for reporting results of additional clinical research about the safety and effectiveness of the unapproved use involved.

To disseminate off-label use information manufacturers were also required to submit a supplemental new drug application to the Secretary, receive certification that they would file a supplemental application based on completed or planned studies, or receive an exemption from submitting such an application. A manufacturer could qualify for an exemption from the requirement to submit a supplemental application in three situations.³³ Exemptions could only have been approved if the Secretary determined that the supplemental application would have been economically prohibitive or if the Secretary determined that it would have been “unethical to conduct the studies necessary for the supplemental application.”³⁴ The Secretary could have terminated such approval at any time and ordered the manufacturer to cease distributing the information.

Legislative History

The legislative history provides some background for the policy reasons for including the provision relating to off-label drug uses. Some of the issues raised prior to the enactment of the now-defunct provision of FDAMA may still pose concerns today:

The conference agreement's inclusion of [§ 401] is intended to provide that health care practitioners can obtain important scientific information about the uses that are not included

³³ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-3(b)-(d)). The manufacturer could either (1) certify that the studies for a supplemental application were complete and that the supplemental application would be submitted within six months after the initial dissemination of the information; or (2) submit a proposed protocol and schedule for studies for the supplemental application that the Secretary has determined were adequate and reasonable, respectively, and certify that the supplemental application would be submitted within 36 months after the initial dissemination of the information; or (3) receive the Secretary's approval for an application for an exemption from the requirement to submit a supplemental application. Manufacturers were also required to submit periodic status reports. If the Secretary determined that the studies could not be completed and submitted within 36 months, or the manufacturer had submitted a written request for an extension and the Secretary determined that the manufacturer had diligently conducted the studies, an extension of up to 24 months could have been provided.

³⁴ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-3(d)(2)).

in the approved labeling of drugs, biological products, and devices. The conferees also wish to encourage that these new uses be included on the product label. Therefore, the agreement includes strong incentives to conduct the research needed and file a supplemental application for such uses.³⁵

The House Report on the earlier House version of the FDAMA, H.R. 1411, remarked on the FDA's jurisdiction and authority with regard to the dissemination of information by manufacturers. The report noted that the agency "has a role to play with respect to assuring balance and objectivity and to protecting the public health."³⁶

Representative Markey, on the other hand, took issue with the off-label provisions:

The drug bill contains a dangerous and precedent-setting provision regarding dissemination of information. The "Off-label" provision could better be described as the "under the table" provision, allowing companies to market a product for unsupported uses that could seriously send thousands of consumers "off the cliff." In putting profits over patient care, this bill opens the door for aggressive promotion of unproven uses of drugs, while giving companies three to five years to produce scientific evidence that these off-label uses are safe and effective....³⁷

The FDA's January 2009 Guidance

The FDA's guidance on good reprint practices was issued in the last few days of the Bush Administration. It contains provisions similar to some of the FDAMA dissemination provisions that expired in 2006, but also appears to expand the ability of the pharmaceutical industry to disseminate such information.

The guidance differs in several ways from the expired FDAMA provisions. The guidance does not include the following, which were present in FDAMA: (1) the requirement for a submission of a supplemental new drug application or the Secretary's approval of an application for an exemption from this requirement;³⁸ (2) the Secretary's ability to require a manufacturer to disseminate (a) additional scientifically sound information to provide objectivity and balance, and (b) a statement from the Secretary on the safety and effectiveness of the unapproved use;³⁹ (3) the Secretary's ability to order the manufacturer to cease dissemination of information in certain situations, such as if the Secretary determined that the unapproved use may not be effective or may present a significant risk to public health, or if the information did not comply with FDAMA's provisions;⁴⁰ (4) provisions that required manufacturers to submit lists of the articles and reference publications that they disseminated and to keep records in case the manufacturer

³⁵ H.Rept. 105-399 (2007) (Conf. Rep.); *see also* H.Rept. 105-310 (Oct. 7, 1997) ("The principal policy considerations that underlie this provision are the facilitation of greater access to timely and accurate information by health care providers.").

³⁶ H.Rept. 105-310 (Oct. 7, 1997). The Senate version of FDAMA (S. 830) did not contain similar provisions regarding dissemination of information on new uses but rather discussed "the danger that policies related to dissemination of health economic information will become an avenue for off-label promotion of unsubstantiated clinical efficiency claims." S.Rept. 105-43 (July 1, 1997).

³⁷ *Id.*

³⁸ *See* Guidance, *supra* note 3; P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-3).

³⁹ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(c)).

⁴⁰ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-4).

was required to take corrective action;⁴¹ (5) the requirement that the manufacturer include, along with the information being disseminated, “a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information being disseminated” and, if applicable, a statement “that the information is being distributed at the expense of the manufacturer”;⁴² (6) the requirement that a copy of the information to be disseminated and clinical trial information regarding the unapproved use be submitted to the Secretary 60 days prior to dissemination;⁴³ (7) the requirement that the article not have unapproved uses of drugs or devices as its primary focus;⁴⁴ and (8) a provision requiring that a scientific or medical journal be a publication “that is generally recognized to be of national scope and reputation.”⁴⁵

However, the guidance also contains new potential safeguards that were not present in FDAMA, such as (1) the recommendation that reprints of scientific articles not be distributed with promotional materials, at promotional exhibit halls, or during promotional speaker events, in addition to not being the topic of discussion during a sales visit by a sales representative to a physician’s office; (2) the recommendation that a journal reprint be accompanied by a statement disclosing “all significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article” and a disclosure of “the manufacturer’s interest in the drug or medical device that is the subject of the journal reprint or reference text”; (3) examples of what would constitute false or misleading information, such as a reprint of an article that is characterized as definitive but “is inconsistent with the weight of credible evidence”; and (4) examples of publications that would not meet the guidance’s recommendations, such as reports of early clinical trials in healthy subjects.⁴⁶

The guidance seemingly creates a safe harbor for dissemination of information on off-label uses of FDA-approved drugs by stating that “if a manufacturer follows [its] recommendations ... the FDA does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in this guidance as establishing intent that the product be used for an unapproved new use.”⁴⁷ While some view the document as shielding a “controversial promotional practice,” others believe the guidance would “probably restrict more aggressive companies.”⁴⁸ Additionally, the document’s issuance, along with a set of proposed rules and other guidance documents, has been criticized by some who are concerned that the FDA may be placing pharmaceutical industry priorities over public health protections for consumers.⁴⁹ Questions have been raised regarding whether the FDA has the authority to issue this guidance document.

⁴¹ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-2).

⁴² P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(b)(6)).

⁴³ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa(b)(4)).

⁴⁴ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-1((b)(4)).

⁴⁵ P.L. 105-115, § 401 (expired 21 U.S.C. § 360aaa-5(5)(C)).

⁴⁶ See Guidance, *supra* note 3.

⁴⁷ *Id.*

⁴⁸ Wilde Mathews and Johnson, *supra* note 11.

⁴⁹ Letter from Henry A. Waxman, Chairman, House Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, FDA, Sept. 17, 2008, at 2, <http://oversight.house.gov/documents/20080917113245.pdf>.

Administrative Law Issues

FDA rules may be subject to legal challenges. This section addresses administrative law principles that may come into play in the event that the FDA's guidance is implemented or enforced in a manner that would render it a binding rule that should have been promulgated under the provisions of the Administrative Procedure Act (APA). Additionally, this section addresses the question of whether the FDA had the authority to issue such a guidance document, due to the expiration of the FDAMA provisions.

Rules and Guidance Documents

Agency rules have the force and effect of law and may be reviewed and invalidated by courts.⁵⁰ Under notice-and-comment rulemaking procedures, agencies must publish notice of a proposed rulemaking in the *Federal Register*, provide opportunity for the submission of comments by the public, and publish a final rule and a general statement of basis and purpose in the *Federal Register* “not less than 30 days before its effective date.”⁵¹ In contrast, guidance documents do not have to undergo notice-and-comment procedures. They do not have the force and effect of law; they are a type of general statement of policy.⁵² General statements of policy are agency statements that “advise the public prospectively of the manner in which the agency proposes to exercise a discretionary power.”⁵³ General statements of policy do not “impose any rights and obligations,”⁵⁴ nor do they “establish a ‘binding norm’” because they do not represent the final determination regarding the issues they address.⁵⁵

Congress has passed requirements specific to FDA guidance documents, which note that such documents “shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration.”⁵⁶ Thus, while the FDA guidance on reprint practices indicates the agency's thoughts on the topic and potentially how the agency itself would use, or rather limit its use of, its enforcement powers—such as criminal and civil penalties, injunctions, and seizures—with regard to the practices outlined in the guidance, the document is not legally binding on courts or persons outside the agency.⁵⁷

A guidance document can become binding on an agency in practice, however. One academic has commented that “[i]n some circumstances, if the language of the document is such that private parties can rely on it as a norm or safe harbor by which to shape their actions, it can be binding as

⁵⁰ 5 U.S.C. §§ 551(4), 701-06; *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020 (D.C. Cir. 2000).

⁵¹ 5 U.S.C. § 553(e), (d).

⁵² JEFFREY S. LUBBERS, *A GUIDE TO FEDERAL AGENCY RULEMAKING* 94 (4th ed. 2006). Executive Order 13422 sets forth a definition of a guidance document. Executive Order 13422, Further Amendment to Executive Order 12866 on Regulatory Planning and Review, Jan. 18, 2007, <http://www.whitehouse.gov/news/releases/2007/01/20070118.html>.

⁵³ Tom C. Clark, Attorney General, *Attorney General's Manual on the Administrative Procedure Act*, at 30 n.3 (1947), <http://www.law.fsu.edu/library/admin/1947iii.html>; see, e.g., *Chamber of Commerce v. United States Department of Labor*, 174 F.3d 206, 212 (D.C. Cir. 1999).

⁵⁴ *Community Nutrition Institute v. Young*, 818 F.2d 943, 946 (D.C. Cir. 1987) (internal quotations omitted).

⁵⁵ *Pacific Gas & Electric Co. v. Federal Power Commission*, 506 F.2d 33 (D.C. Cir. 1974).

⁵⁶ 21 U.S.C. § 371(h). The provisions on guidance documents were added in 1997 by FDAMA § 405.

⁵⁷ Guidance, *supra* note 3.

a practical matter.”⁵⁸ If a policy statement is implemented in a manner that is binding on the agency and outside parties, it will be regarded as a rule and will be deemed invalid for failing to comply with APA notice and comment procedures.⁵⁹ APA procedural requirements do not apply to “interpretive rules, general statements of policy, or rules of agency organization, procedure, or practice,” unless such documents are, in fact, binding, substantive rules.⁶⁰

Is the Guidance a Substantive Rule Subject to a Notice-and-Comment Rulemaking?

This dynamic raises the question as to whether the FDA’s guidance will be implemented in a manner that will in fact render it a rule that must have been promulgated under the notice-and-comment procedures in the APA. Since the guidance document was recently issued, it is not clear how the agency and the pharmaceutical industry will use the document. Additionally, the FDA under the Obama Administration may approach this issue differently than the Bush Administration.⁶¹

If the FDA treats the guidance document as both prospective and voluntary, and as a policy that preserves the agency’s discretion, then the document will not likely be considered a substantive rulemaking document that needs to follow APA notice-and-comment procedures nor be considered to be in violation of the APA. If the FDA uses the guidance document in a manner that constitutes the agency’s implementation of a substantive rule, then a reviewing court could determine that the FDA would be in violation of the APA requirements for notice-and-comment rulemaking. A reviewing court would examine whether the document has a binding effect,⁶² whether the agency retains its ability to exercise discretion,⁶³ whether the document uses voluntary or mandatory language,⁶⁴ and whether the FDA characterizes the document as guidance,⁶⁵ in order to determine if the guidance document is in fact a substantive rule.

⁵⁸ Professor Robert A. Anthony (quoted in LUBBERS, *supra* note 52, at 100); see also Robert A. Anthony, *Interpretive Rules, Policy Statements, Guidances, Manuals, and the Like—Should Agencies Use Them to Bind the Public?*, 41 Duke L. J. 1463 (1992).

⁵⁹ *Bellarm Int'l v. Food and Drug Administration*, 678 F. Supp. 410 (E.D.N.Y. 1988).

⁶⁰ 5 U.S.C. § 553(b). Some agencies have been criticized for using guidance documents to “issue or amend [their] real rules, i.e., [their] interpretative rules and policy statements, quickly and inexpensively without following any statutorily prescribed procedures.” *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020 (D.C. Cir. 2000) (quoting Richard J. Pierce, Jr., *Seven Ways to Deossify Agency Rulemaking*, 47 ADMIN. L. REV. 59, 85 (1995)).

⁶¹ Neither of the two Obama Administration memoranda issued to the heads of executive departments and agencies (regarding steps to be taken with regard to various proposed and final regulations issued in the last few months of the Bush Administration) applies to this guidance document because guidance documents are not addressed in such memoranda. Memorandum from Rahm Emanuel, White House Chief of Staff and Assistant to the President, White House (Jan. 20, 2009), <http://edocket.access.gpo.gov/2009/pdf/E9-1639.pdf>; Memorandum from Peter R. Orszag, Director, Office of Management and Budget (Jan. 21, 2009), http://www.whitehouse.gov/omb/assets/agencyinformation_memoranda_2009_pdf/m09-08.pdf.

⁶² “If an agency acts as if a document issued at headquarters is controlling in the field, if it treats the document in the same manner as it treats a legislative rule, if it bases enforcement actions on the policies or interpretations formulated in the document, if it leads private parties or State permitting authorities to believe that it will declare permits invalid unless they comply with the terms of the document, then the agency’s document is for all practical purposes ‘binding.’” *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1021 (D.C. Cir. 2000).

⁶³ *American Bus Ass’n v. United States*, 627 F.2d 525, 529 (D.C. Cir. 1980); see also *Chamber of Commerce v. United States Department of Labor*, 174 F.3d 206, 212 (D.C. Cir. 1999).

⁶⁴ Courts have held that the language an agency uses can determine whether a document is a general statement of policy (continued...)

Additionally, some have argued that a guidance document can become “binding as a practical matter” in some cases “if the language of the document is such that private parties can rely on it as a norm or safe harbor by which to shape their actions.”⁶⁶ It is not known how the pharmaceutical industry would rely on the guidance document, although the document itself is similar in many respects to the FDAMA provisions that Congress did not renew in 2006. Presumably, the pharmaceutical industry could have relied on the FDAMA provisions and the FDA’s implementing regulations while they were in effect, in order for the manufacturer’s distribution of reprints regarding off-label uses not to be used in an enforcement case as evidence of the manufacturer’s intent that a drug be used for an unapproved, off-label use.⁶⁷ Therefore, it seems that pharmaceutical manufacturers could attempt to use the FDA guidance as a safe harbor when distributing a peer-reviewed article.

Does the FDA Have the Authority to Issue the Guidance?

Additionally, the question arises as to whether the FDA has the authority to issue such guidance because Congress had given the agency explicit authority on this topic in FDAMA but then did not renew the provisions granting the agency that authority. In a letter to the FDA Commissioner, Representative Waxman described the FDA’s issuance of the guidelines, in draft form, as “an effort by FDA to displace Congress and establish by administrative fiat a new system for use of journal articles that lacks the safeguards set by Congress.”⁶⁸ A reviewing court would examine the FFDCa, “and the ever-evolving statutory scheme, recognizing that the [FFDCa]’s meaning may be affected by other Acts, particularly where Congress has spoken subsequently and more specifically to the topic at hand.”⁶⁹

(...continued)

or a substantive rule: While the agency’s characterization of an official statement as binding or nonbinding has been given some weight, of far greater importance is the language used in the statement itself. We have, for example, given decisive weight to the agency’s choice between the words “may” and “will.” In holding that a declaration of the Interstate Commerce Commission was *not* a general statement of policy, we relied upon the fact that the pronouncement at issue declared that “the Commission *will*” make certain demands of applicants for particular certificates; while in holding that a pronouncement of the Federal Savings and Loan Insurance Corporation was nothing more than a general statement of policy, we relied upon the use of the word “may” in its description of the agency’s intended future course. *Brock v. Cathedral Bluffs Shale Oil Co.*, 796 F.2d 533, 537-38 (D.C. Cir. 1986) (internal citations omitted); *see also* *Community Nutrition Institute v. Young*, 818 F.2d 943, 947 (D.C. Cir. 1986).

⁶⁵ In *Professionals and Patients for Customized Care v. Shalala*, the court noted that the FDA’s consistent classification of a document as a policy statement was one factor “in favor of a holding that [a compliance policy guide was] not a substantive rule.” 56 F.3d 592, 596 (5th Cir. 1995).

⁶⁶ Professor Robert A. Anthony (quoted in LUBBERS, *supra* note 52, at 100); *see also* Robert A. Anthony, *Interpretive Rules, Policy Statements, Guidances, Manuals, and the Like—Should Agencies Use Them to Bind the Public?*, 41 Duke L. J. 1463 (1992).

⁶⁷ *See* Guidance, *supra* note 3. According to House Oversight and Government Reform Committee Chairman Henry Waxman, “[d]uring the period between enactment in 1997 and 2006, a number of abuses involving journal articles occurred, including the abuses involving anti-depressants, Vioxx, Celebrex, and Neurontin described in this document.” Letter from Henry A. Waxman, Chairman, House Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, FDA, Nov. 30, 2007, at 5, <http://oversight.house.gov/documents/20071130102744.pdf>.

⁶⁸ Letter from Henry A. Waxman, Chairman, House Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, FDA, Nov. 30, 2007, at 5, <http://oversight.house.gov/documents/20071130102744.pdf>.

⁶⁹ *Ass’n of American Physicians Surgeons, Inc. v. United States*, 226 F. Supp. 2d 204, 212 (D.D.C. 2002) (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000)) (internal quotations omitted).

The FDA could assert that its general statutes and regulations grant it such authority.⁷⁰ FDCA § 701(h)(5) required the FDA to issue regulations on the agency's policies for developing, issuing, and using guidance documents.⁷¹ FDA regulations on good guidance practices define a "guidance document" to include "documents that relate to: The ... labeling [and] promotion ... of regulated products ... and inspection and enforcement policies."⁷² The FDA's guidance on reprint practices would appear to fall within the definition of a guidance document, as it relates to labeling and promotion of unapproved new uses of FDA-approved drugs and medical devices. The FDA can also assert that it has attempted to address dissemination of information on off-label uses even prior to FDAMA.⁷³ For example, in 1992, the FDA issued a notice asking for comment on a draft policy statement regarding "the categories of educational activities that may continue to be funded by industry and yet avoid regulation as advertising or promotional labeling."⁷⁴ It noted that "[t]he companies' programs and materials are subject to the labeling and advertising provisions of the act."⁷⁵ Thus, based on these statutes and regulations, it would appear that the FDA is acting on a legally tenable basis in issuing the guidance on the reprint practices.

Since the FDA's guidance document does not have the force of law, to the extent that it is challenged, it would not receive the same degree of deference as a substantive rule promulgated under the APA notice and comment procedures.⁷⁶ To the extent that the guidance document receives deference by a reviewing court, that deference would be of the type elucidated in *Skidmore v. Swift & Co.*:

[T]he rulings, interpretations and opinions of [the agency], while not controlling upon the courts by reason of their authority, do constitute a body of experience and informed judgment to which courts and litigants may properly resort for guidance. The weight of such a judgment in a particular case will depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control.⁷⁷

⁷⁰ FDCA § 701(h) states that "[t]he Secretary shall develop guidance documents with public participation," and provides that "[f]or guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation of guidance documents." 21 U.S.C. §§ 371(h)(1)(A) and (C).

⁷¹ 21 U.S.C. § 371(h)(5).

⁷² 21 C.F.R. § 10.115(b)(2).

⁷³ The FDA's previous assertion of jurisdiction in this area could be contrasted with the agency's "express[] disavow[al]" of jurisdiction to regulate tobacco products, which the Supreme Court documented in *FDA v. Brown & Williamson Tobacco Corp.* In that case, the FDA shifted its long-held position with regard to whether it had authority to regulate tobacco. The Court held that "the FDA's assertion of jurisdiction is impermissible" in light of congressional intent to the contrary, as expressed in "the FDCA's overall regulatory scheme and in the tobacco-specific legislation that it has enacted subsequent to the FDCA." 529 U.S. 120, 125-26 (2000). Given these factors, the sunset of FDAMA does not necessarily indicate that Congress meant to keep the FDA from acting on its own authority.

⁷⁴ FDA, Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 Fed. Reg. 56412 (Nov. 27, 1992).

⁷⁵ *Id.*

⁷⁶ See *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944).

⁷⁷ *Id.*; see also *Christensen v. Harris County*, 529 U.S. 576, 587 (2000); *Ohio Pub. Employees Retirement System v. Betts*, 492 U.S. 158, 171 (1989) ("no deference is due to agency interpretations at odds with the plain language of the statute itself").

In other words, courts will often give weight to an agency's interpretations, due to the agency's "specialized experience" in the administration of its given functions.⁷⁸ Such agency documents are entitled to a "respect proportional to [their] 'power to persuade.'"⁷⁹ In the guidance document, the FDA appears to be loosening the standards passed by Congress on off-label marketing, without regard to the sunset of the FDAMA provisions on the dissemination of information regarding off-label uses in 2006 and subsequent congressional silence.⁸⁰ Therefore, a court may give less deference to the agency or find the guidance document unpersuasive due to its lack of consistency with earlier agency positions, in particular, those mandated by Congress.

In a case addressing an agency's jurisdiction, when a specific statutory provision prohibited the Federal Communications Commission (FCC) from having jurisdiction over certain intrastate communication services, but the agency attempted to exercise its jurisdiction in that area regardless, the Supreme Court stated the following:

[A]n agency literally has no power to act ... unless and until Congress confers power upon it.... Thus, we simply cannot accept an argument that the FCC may nevertheless take action which it thinks will best effectuate a federal policy. An agency may not confer power upon itself. To permit an agency to expand its power in the face of a congressional limitation on its jurisdiction would be to grant to the agency power to override Congress.⁸¹

Although Congress did not enact a specific statute prohibiting the FDA from addressing reprint practices, it is conceivable that some might assert the agency's action—in light of Congress's decision to legislate the sunset of the off-label provisions—could be viewed as an attempt by the FDA to alter federal policy in the area.⁸² Alternately, the FDA's statutes appear to grant the agency authority to issue guidance documents relating to promotion of FDA-regulated products. The congressional silence in this area since the sunset of FDAMA stands in contrast to other cases where Congress has considered and rejected bills on the subject.⁸³

First Amendment Challenges

Assuming that the FDA has the authority to issue the guidance, these provisions may face a First Amendment challenge. FDAMA § 401 and the earlier 1996 FDA guidance documents (both of which addressed permissible methods for the dissemination of information about "off-label" uses by drug manufacturers) have been challenged on First Amendment grounds. The U.S. District Court for the District of Columbia initially found that these provisions violated the First

⁷⁸ *United States v. Mead Corp.*, 533 U.S. 218, 234 (2001).

⁷⁹ *Id.* at 235 (quoting *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944)).

⁸⁰ *See e.g.* *Whitman v. Am. Trucking Ass'n, Inc.*, 531 U.S. 457 (2001); *see, e.g.*, *Sullivan v. Zebley*, 493 U.S. 521 (1990) (finding regulations "are simply inconsistent with the statutory standard"); *Dole v. Steelworkers*, 494 U.S. 26 (1990) (foreclosing deference to OMB's interpretation of the Paperwork Reduction Act because the Court held that there was clear congressional intent to the contrary).

⁸¹ *La. Pub. Serv. Comm'n v. FCC*, 476 U.S. 355, 374-75 (1986).

⁸² *See Ass'n of American Physicians Surgeons, Inc. v. United States*, 226 F. Supp. 2d 204 (D.D.C. 2002) (finding that the FDA's pediatric rule exceeded the authority delegated to the agency by Congress because the specific statutory provisions in the FFDCA did not provide a "sound basis" for the rule and because it was incompatible with the Best Pharmaceuticals for Children Act (BPCA), although Congress did not explicitly reject the pediatric rule in enacting BPCA).

⁸³ *See, e.g.*, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 155, 159-60 (2000).

Amendment and issued an injunction.⁸⁴ However, subsequent developments at the Court of Appeals level caused the injunction to be vacated, leaving the constitutional question open.⁸⁵ This section will briefly describe these cases.

The Washington Legal Foundation (WLF), a nonprofit group that advocates against excessive government regulation, challenged earlier FDA guidance documents (issued in 1996) dealing with the distribution of enduring materials⁸⁶ by drug manufacturers. In particular, the WLF argued that the FDA was impermissibly restricting constitutionally protected speech.⁸⁷ The district court in *WLF v. Friedman (WLF I)* determined that the FDA was restricting protected speech, but that the speech was entitled to a lower degree of constitutional protection because it was commercial in nature (rather than wholly scientific or academic, as WLF argued).⁸⁸ In order for a restriction on commercial speech to be constitutional, the restriction must satisfy a four-part test.⁸⁹

The first question addressed in the four-part test is whether the speech covered by the restriction is false, misleading, or concerns an illegal activity.⁹⁰ The First Amendment does not protect commercial speech concerning unlawful activities or false or deceptive advertising.⁹¹ The district court in *WLF I* determined that the speech addressed by the FDA guidance did not concern an illegal activity, because the speech being distributed by the drug manufacturers “address[ed] using FDA-approved drugs to treat conditions and in treatment regimens other than those set forth in the label approved by the FDA,” an activity that is not unlawful.⁹² A closer question for the court was the whether the speech could be deemed false or misleading. Here, the court looked at whether the information being distributed could be characterized as “inherently misleading.”⁹³ In making its determination, the court looked at the controls available to the FDA concerning the information that may be distributed by the manufacturers.⁹⁴ The court found that these controls

⁸⁴ *Washington Legal Foundation v. Friedman*, 13 F.Supp. 2d 51, 54 (D.D.C. 1998) (“WLF I”).

⁸⁵ It should be noted that the cases discussed in this section analyze the constitutionality of regulatory guidance and statutory provisions that are no longer in force. These cases, however, may be referenced by a court that is evaluating the constitutionality of current guidance due to the similarities between the previous scheme and the recently issued guidance documents.

⁸⁶ Enduring materials are reprints of medical textbooks and peer-reviewed journal articles. *WLF I*, 13 F.Supp. 2d at 51 (internal citations omitted).

⁸⁷ *WLF I*, 13 F.Supp. 2d at 54.

⁸⁸ *Id.* at 62-65.

⁸⁹ *Central Hudson Gas and Electric Corp. v. Public Service Comm’n of New York*, 447 U.S. 557 (1980).

⁹⁰ *In re R.M.J.*, 455 U.S. 191, 200 (1982) (“False, deceptive or misleading advertising remains subject to restraint.”).

⁹¹ *Pittsburgh Press Co. v. Pittsburgh Comm’n on Human Relations*, 413 U.S. 376, 37 L. Ed. 2d 669, 93 S. Ct. 2553 (1973).

⁹² *WLF I*, 13 F.Supp. 2d at 66. The FDA argued that the speech at issue in this case could not survive the first prong of the constitutional test, because when a manufacturer promotes a drug for an unapproved use the manufacturer may be engaged in misbranding, which is illegal. The court rejected this argument. The court found that the proper test was not whether the speech at issue violated a law or regulation, but whether the speech promoted conduct that is illegal. Because the speech in this case promotes conduct that is legal (that is the “off-label” prescription of drugs), the speech does not promote illegal activities. *Id.* However, if Congress were to ban the prescription of drugs for off-label uses, the free speech analysis of this question would change, as speech regarding off-label uses of FDA-approved drugs would then concern an illegal activity.

⁹³ *WLF I*, 13 F.Supp. 2d at 67 (“In order to end the *Central Hudson* analysis on the first prong, the speech must be ‘inherently misleading,’ which is defined in *Central Hudson* as ‘more likely to deceive the public than to inform it.’” *Central Hudson*, 447 U.S. at 563.”)

⁹⁴ *WLF I*, 13 F.Supp. 2d at 67.

circumscribed the possibility that untruthful or misleading information could be disseminated by manufacturers. As a result, the court did not consider the speech to be inherently misleading. The speech at issue, therefore, is entitled to some degree of First Amendment protection.

In order to determine whether the FDA's policies were a constitutionally permissible restriction on commercial speech, the court proceeded to the next three steps of the constitutional analysis: (1) whether the government has a substantial interest in imposing the restriction on speech; (2) whether the restriction at issue directly advances that interest; and (3) whether the restriction at issue is not more extensive than necessary to achieve that interest.

The court found that the government does have a substantial interest in encouraging drug manufacturers to get off-label treatments on-label, as many uses for drugs that have been approved in other treatment contexts would otherwise evade the FDA approval process (a process that Congress has declared *all* uses for drugs should endure).⁹⁵ The court also found that restricting marketing options for off-label uses of approved drugs advances this interest, because it is "one of the few mechanisms available to the FDA to compel" manufacturers to seek FDA approval for off-label uses (considering that the conventional mechanism of preventing the drug from being introduced into interstate commerce is unavailable because FDA-approved drugs may be introduced into interstate commerce, regardless of whether they will be prescribed for an off-label use or an FDA-approved use).⁹⁶

However, the court found that the guidance documents at issue in this case were nonetheless unconstitutional, because they were, in the court's estimation, more extensive than necessary to achieve the stated interest.⁹⁷ Though, under a commercial speech analysis, the government need not choose the least restrictive method for achieving its goal, an effort must be made to create a reasonable fit between the method chosen and the ends sought.⁹⁸ If a commercial speech restriction burdens substantially more speech than necessary, courts will not allow the restriction to take effect.⁹⁹ The district court, finding that the FDA guidance burdened substantially more speech than necessary, cited at least one alternative method that the government could have used to achieve its objectives, which placed a significantly smaller burden on protected speech.¹⁰⁰ For example, the court hypothesized that requiring complete and unambiguous disclosure by manufacturers who would disseminate the information at issue would be equally effective in achieving the government's goal and would place a lesser burden on speech.¹⁰¹

As a result, the court held that while the government may restrict drug manufacturer promotion of off-label uses, the restrictions in the guidance documents were too extensive to withstand constitutional scrutiny. The district court issued an injunction barring the FDA from prohibiting, restricting, or sanctioning drug manufacturers "for disseminating or redistributing to physicians or other medical professionals any article concerning prescription drugs or medical devices previously published in a bona fide peer-reviewed professional journal, regardless of whether such article includes a significant or exclusive focus on uses of drugs or medical devices other

⁹⁵ *Id.* at 70-71.

⁹⁶ *Id.* at 72.

⁹⁷ *Id.*

⁹⁸ *Board of Trustees of the State University of New York v. Fox*, 492 U.S. 469, 478 (1989).

⁹⁹ *United States v. Edge Broadcasting Co.*, 509 U.S. 418, 430 (1993).

¹⁰⁰ *WLF I*, 13 F.Supp. 2d at 73.

¹⁰¹ *Id.*

than those approved by FDA and regardless of whether such article reports the original study on which FDA approval of the drug or device in question was based.”¹⁰²

Following the issuance of this injunction, which applied to the guidance documents of 1996, FDAMA took effect in 1997 and superseded the guidance documents. The district court amended its injunction to clarify that the injunction applied with equal force to FDAMA. Though some aspects of FDAMA were different from the previous guidance documents, the court ultimately determined that the underlying policies in FDAMA largely duplicated those of the guidance documents and were unconstitutional for similar reasons.¹⁰³ The FDA appealed.

The U.S. Court of Appeals for the District of Columbia described the parties’ briefs in this case as “confusing.”¹⁰⁴ The fundamental disconnect in the opposing parties’ arguments became clear only at oral argument. WLF, in briefings and at oral argument, challenged the FDA’s guidance documents under the theory that the FDA was banning *independently* the manufacturer dissemination of enduring materials on off-label uses and that proof of such dissemination would *alone* justify enforcement action. The FDA, however, asserted at oral argument that the FDAMA provided a “safe harbor” for the dissemination of such information, and that “the agency would draw *no independent* prosecutorial authority from the FDAMA to buttress any enforcement proceeding.”¹⁰⁵ The FDA, though reserving the right to use such promotional conduct as evidence in a misbranding or “intended use” enforcement action, claimed no independent authority to regulate speech through the FDAMA.

Because both parties, at that point, agreed that there was no constitutional controversy, the court of appeals declined to rule on the constitutionality of the provisions at issue. Furthermore, since no controversy over the FDA’s newly clarified interpretation existed, the court vacated the injunction that declared FDAMA to be unconstitutional and dismissed the FDA’s appeal. In disposing of the case in such a manner, the court noted that it was not criticizing or overruling the reasoning of the district court on the First Amendment issue as it had been presented to the district court. The appeals court also made clear that a manufacturer may still bring suit in order to argue that the FDA’s use of a manufacturer’s promotion of off-label uses as evidence in an enforcement action violates the First Amendment.¹⁰⁶

In the guidance document released earlier this year, the FDA appears to create a “safe harbor” similar to that which was previously in place under FDAMA.¹⁰⁷ The FDA does not claim to draw independent enforcement authority from violations of the guidance. Instead, the agency said that it does not intend to consider information distributed in compliance with the guidance documents as “establishing intent that the product be used for an unapproved new use.”¹⁰⁸ The FDA reserves the right to consider information that is distributed outside the parameters of the guidance as evidence in establishing such intent, however. In light of this, a manufacturer (or any other plaintiff with standing to sue) may challenge under the First Amendment the FDA’s use of off-

¹⁰² *Id.* at 74.

¹⁰³ *See* Washington Legal Foundation v. Friedman, 36 F.Supp. 2d 16 (D.D.C. 1999)(“WLF II”); Washington Legal Foundation v. Henney, 56 F.Supp. 2d 81 (D.D.C. 1999)(“WLF III”).

¹⁰⁴ Washington Legal Foundation v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000).

¹⁰⁵ *Id.* at 336.

¹⁰⁶ *Id.* at 336-37, n. 6, n. 7.

¹⁰⁷ *See* Guidance, *supra* note 3.

¹⁰⁸ *Id.*

label promotion as evidence in other enforcement actions.¹⁰⁹ If the speech is used as evidence to establish an element of a violation which itself is a restriction on lawful commercial speech, that violation may also be challenged on First Amendment grounds.

False Claims Act Issues

The False Claims Act

The FDA's new guidance regarding the promotion of off-label drug uses may also raise issues under the False Claims Act. Under the FCA, any person who "knowingly presents, or causes to be presented, ... a false or fraudulent claim for payment or approval" to the United States government may be subject to civil penalties.¹¹⁰ Penalties under the FCA include treble damages, plus an additional penalty of \$5,500 to \$11,000 for each false claim filed.

Civil actions may be brought in federal district court under the False Claims Act by the Attorney General or by a whistleblower, for the person and for the U.S. Government, in what is termed a *qui tam* action. The ability to initiate a *qui tam* action has been viewed as a powerful weapon against fraud, in that it may be initiated by a private party who may have direct and independent knowledge of any wrongdoing.¹¹¹ The popularity of *qui tam* actions brought under the FCA may be attributed partially to the fact that successful whistleblowers can receive between 15% and 30% of the monetary proceeds of the action or settlement that are recovered by the government.¹¹²

False Claims Act Cases Involving Off-Label Promotion

In the context of manufacturer promotion of off-label uses of drugs, several *qui tam* actions have been brought in recent years using the FCA. One of the largest settlements resulted from a case

¹⁰⁹ See *WLF IV*, 202 F.3d at 336-37, n. 6. Such a challenge may be difficult to maintain in light of *Wisconsin v. Mitchell*, 508 U.S. 476 (1993). In that case, the Supreme Court held that "the First Amendment ... does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." *Id.* at 489.

¹¹⁰ 31 U.S.C. § 3729. For additional discussion of the FCA, see CRS Report RL30463, *Constitutional Aspects of Qui Tam Actions: Background and Analysis of Issues in Vermont Agency of Natural Resources v. United States ex rel. Stevens*, by (name redacted) and CRS Report RS22744, *Health Care Fraud and Abuse Laws Covering Medicare and Medicaid: An Overview*, by Jennifer Staman. The government may be able to bring an action for a false claim under several statutes other than the False Claims Act. See, e.g., 18 U.S.C. § 1347.

¹¹¹ Health Law, 50 (Barry Furrow 2d ed. 2000).

¹¹² Prosecution under the FCA may also be more attractive for the government. It has been pointed out that the terms of the act are relatively simple and straightforward, and can be applied generally to healthcare providers. See Dayna Bowen Matthew, *An Economic Model to Analyze the Impact of False Claims Act Cases on Access to Healthcare for the Elderly, Disabled, Rural and Inner-City Poor*, 27 AM. J. L. AND MED. 439 (2001). Furthermore, because the FCA is a civil statute, there is an easier burden of proof to meet (preponderance of the evidence) than there would be in a criminal statute (beyond a reasonable doubt). *Id.*

However, the government has also achieved successful results outside of the FCA by alleging misbranding alone. In December 2005, Eli Lilly and Company plead guilty to criminal misbranding of the osteoporosis drug Evista under the FDCA and paid fines and equitable disgorgement totaling \$36 million. Eli Lilly allegedly "promoted Evista as effective for reducing the risk of breast cancer, even after Lilly's proposed labeling for this use was specifically rejected by the FDA." DOJ, Press Release, Eli Lilly and Company to Pay U.S. \$36 Million Relating to Off-Label Promotion, Dec. 21, 2005, http://www.usdoj.gov/opa/pr/2005/December/05_civ_685.html.

brought by a whistleblower named Dr. David Franklin against his former employer, Warner-Lambert Co., a pharmaceutical company.¹¹³ In that case, Franklin alleged that Warner-Lambert promoted off-label uses of the drug Neurontin, and that such promotion “caused the submission of false claims to the Veterans Administration and to the federal government for Medicaid reimbursement.”¹¹⁴ The court in that case explained the interaction of off-label prescribing and Medicaid reimbursement:

Reimbursement under Medicaid is, in most circumstances, available only for “covered outpatient drugs.” 42 U.S.C. § 1396b(i)(10). Covered outpatient drugs do not include drugs that are “used for a medical indication which is not a medically accepted indication.” *Id.* § 1396r-8(k)(3). A medically accepted indication, in turn, includes a use “which is approved under the [FFDCA]” or which is included in a specified drug compendia. *Id.* § 1396r-8(k)(6). See also *id.* § 1396r-8(g)(1)(B)(i) (identifying compendia to be consulted). Thus, unless a particular off-label use for a drug is included in one of the identified drug compendia, a prescription for the off-label use of that drug is not eligible for reimbursement under Medicaid.¹¹⁵

Neither Neurontin, or Accupril, another drug for which Warner-Lambert’s marketing practices were at issue, had off-label uses that were present in the indicated compendia.¹¹⁶ Neurontin had only been approved by the FDA for use in conjunction with other drugs “to control seizures in people with epilepsy.”¹¹⁷ However, Dr. Franklin alleged that Warner-Lambert sales representatives called “medical liaisons” were trained to discuss reports of Neurontin’s effectiveness as a mono-therapy to treat epilepsy, meaning the use of Neurontin without the other drugs with which its safety and effectiveness had been presented to FDA.¹¹⁸ The medical liaisons also allegedly reported that the use of the drug for bipolar disease, pain syndromes, and attention deficit disorders was effective according to clinical trials and other reports, though no such data existed.¹¹⁹

The case settled and did not go to trial. Pfizer, which merged with Warner-Lambert, paid criminal monetary penalties for its violations of the FFDCA and civil monetary penalties for its violations of the FCA totaling \$430 million. Pfizer pled guilty to two felony violations of the FFDCA—one for misbranding due to a failure to give adequate directions for use¹²⁰ and one for introducing an

¹¹³ United States ex rel. Franklin v. Warner-Lambert Co., 147 F. Supp. 2d 39 (D. Mass. 2001).

¹¹⁴ *Id.* at 43.

¹¹⁵ *Id.* at 44-45. The court also noted that “[p]ayment for certain drugs that are not otherwise covered may be allowed where the drugs have been determined to be ‘essential to the health of beneficiaries.’ 42 U.S.C. § 1396r-8(a)(3).” For a drug to be covered under that exception, it must also “ha[ve] been given a rating of 1-A by the Food and Drug Administration; and ... the physician has obtained approval for use of the drug in advance of its dispensing in accordance with a prior authorization program.” *Id.* at 45. It does not seem that most cases potentially brought under the FCA would meet these requirements.

¹¹⁶ *Id.*; DOJ, Press Release, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion, May 13, 2004, http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm; FDA, Drug Maker to Pay \$430 Million in Fines, Civil Damages, FDA Consumer Magazine, (July - Aug. 2004) http://www.fda.gov/fdac/features/2004/404_wl.html.

¹¹⁷ FDA, *supra* note 116.

¹¹⁸ See *Franklin*, 147 F. Supp. 2d at 48.

¹¹⁹ *Id.* at 48-49.

¹²⁰ FDA, Drug Maker to Pay \$430 Million in Fines, Civil Damages, FDA Consumer Magazine, (July - Aug. 2004), http://www.fda.gov/fdac/features/2004/404_wl.html; 21 U.S.C. § 331(a).

unapproved new drug in interstate commerce¹²¹—for which it agreed to pay a \$240 million criminal fine.¹²² Additionally, the company paid the United States government \$83.6 million, plus interest, for its civil liability under the FCA for Medicaid reimbursement claims;¹²³ \$68.4 million, plus interest, to the states and the District of Columbia for state Medicaid losses; and \$38 million, plus interest, “for harm caused to consumers and to fund a remediation program to address the effects of Warner-Lambert’s improper marketing scheme.”¹²⁴ Finally, Pfizer agreed to a corporate integrity agreement that addresses the “training and supervising [of] its marketing and sales staff, and ensures that any future off-label marketing conduct is detected and corrected on a timely basis.”¹²⁵

The Warner-Lambert court’s reasoning is similar to that presented in other FCA suits related to marketing of off-label drug uses for which Medicaid, Medicare, or a governmental entity reimbursed the claims that were false because of the off-label use. For example, in a separate FCA *qui tam* case, the U.S. government alleged that the pharmaceutical manufacturer Cell Therapeutics, Inc., “made false and misleading statements to treating doctors to the effect that [an acute promyelocytic leukemia drug] Trisenox was medically accepted for the off-label uses being promoted, and therefore eligible for Medicare reimbursement.”¹²⁶ The whistleblower in this case was a former sales representative who alleged that the manufacturer unlawfully marketed Trisenox for diseases such as chronic myeloid leukemia to physicians who had rarely, if ever, treated patients with the disease (acute promyelocytic leukemia) for which use of the drug was FDA-approved.¹²⁷

The manufacturer allegedly caused false and misleading statements about the drug’s indications to appear in a medical bulletin that doctors use to find answers regarding Medicare reimbursement; the manufacturer’s sales representatives then distributed thousands of copies of the bulletin to doctors to “mislead physicians into mistakenly believing that off-label Trisenox prescriptions were medically accepted and reimbursable.”¹²⁸ The government alleged that the false statements resulted in Trisenox being misbranded and that the company had shipped it as an unapproved new drug in interstate commerce, both violations of the FFDCA.¹²⁹ The Department

¹²¹ 21 U.S.C. § 331(d).

¹²² DOJ, Plea Agreement, Re: Warner-Lambert Company LLC, <http://f1.findlaw.com/news.findlaw.com/hdocs/docs/pfizer/usw151304plea.pdf>. The plea agreement included an estimate that the company gained \$150 million.

¹²³ DOJ, Settlement Agreement and Release, United States ex rel. Franklin v. Warner-Lambert Co., <http://www.usdoj.gov/civil/foia/elecread/2004/Pfizer%20Inc.%202004.pdf>.

¹²⁴ DOJ, Press Release, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion, May 13, 2004, http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.

¹²⁵ *Id.*

¹²⁶ United States ex rel. James Marchese v. Cell Therapeutics, Inc., Civil Action No. 06-168-MJP (W.D. Wash complaint in intervention filed Apr. 16, 2007), at 2. “Trisenox was not approved by the FDA for any indication other than” the treatment of acute promyelocytic leukemia. *Id.* at 10. Medicare Part B provides for only very limited coverage of drugs, but does permit reimbursement for certain off-label uses of FDA-approved drugs or biologicals employed in an anticancer chemotherapeutic regimen if such use is included in a recognized compendium or if the local Medicare contractor determines it to be medically accepted based on clinical evidence from peer-reviewed literature recognized by the HHS Secretary. *See* § 1861(t) of the Social Security Act, 42 U.S.C. § 1395x(t).

¹²⁷ *Marchese*, complaint, at 6, 19, 25.

¹²⁸ *Marchese*, complaint in intervention, at 15. The government alleged that Cell Therapeutics “caused a series of separate false statements to be made to medical directors working for Medicare program carriers to try to obtain Medicare reimbursement for off-label uses of Trisenox.” *Id.* at 2.

¹²⁹ *Id.*

of Justice settled the case for \$10.5 million, plus interest, in April 2007, without the company admitting wrongdoing, but rather asserting that its “statements were a consequence of negligent advice provided” by an outside party.¹³⁰

In another FCA suit, Jazz Pharmaceuticals, Inc., settled with the Department of Justice for \$20 million in civil and criminal penalties and restitution in July 2007. This FCA suit was brought by a former sales representative and addressed the company’s promotion of Xyrem—a drug also known as the date-rape drug or GHB (gamma-hydroxybutyrate)—for off-label uses other than the two approved medical uses related to narcolepsy.¹³¹ The company’s subsidiary pled guilty to criminal misbranding under the FFDCA, through which it led doctors to prescribe Xyrem though such prescriptions were not reimbursable by private insurers, Medicare, or Medicaid.¹³² The Xyrem case also concerned the distribution of documents regarding unapproved new uses that did not follow FDA guidance regarding manufacturer promotion.¹³³

Interaction of the FDA Guidance with the False Claims Act

One question that arises in the context of promotion of off-label drug uses is whether the new FDA guidance might be used to create a safe harbor for pharmaceutical companies if they are sued under the FCA. Although the guidance document is not a statute and may not be binding, this report will first analyze it as if it created a question of statutory construction, as this may help to show how a court may view the role of the guidance document in a FCA case based on marketing or promotion by a pharmaceutical company that arguably falls within the purported safe harbor of the guidance document.¹³⁴

Conflicts frequently arise between the operation of two federal statutes that are silent as to their relationship. In such a case, courts will try to harmonize the two so that both can be given effect. A court “must read [two allegedly conflicting] statutes to give effect to each if [it] can do so while preserving their sense and purpose.”¹³⁵ Only if provisions of two different federal statutes are “irreconcilably conflicting,”¹³⁶ or “if the later act covers the whole subject of the earlier one and is clearly intended as a substitute,”¹³⁷ will courts apply the rule that the later of the two prevails. “[R]epeals by implication are not favored, ... and will not be found unless an intent to repeal is clear and manifest.”¹³⁸ Generally, if Congress intends one statute to repeal an earlier statute or section of a statute, or intends the earlier statute to remain in effect, it usually says so directly in the repealing act.

¹³⁰ United States ex rel. James Marchese v. Cell Therapeutics, Inc., Civil Action No. 06-168-MJP (W.D. Wash. stipulation of dismissal and motion to lift seal filed Apr. 16, 2007), at 4.

¹³¹ United States ex rel. Lauterbach v. Orphan Medical Inc., Civ. Action No. 05-00387 (E.D.N.Y. settlement announced July 13, 2007).

¹³² The United States Attorney’s Office, Eastern District of New York, Press Release, Jazz Pharmaceuticals, Inc. Agrees to Pay \$20 Million to Resolve Criminal and Civil Allegations in “Off-Label” Marketing Investigation, July 13, 2007, <http://www.usdoj.gov/usao/nye/pr/2007/2007jul13a.html>.

¹³³ *Id.*

¹³⁴ For more information, see CRS Report 97-589, *Statutory Interpretation: General Principles and Recent Trends*.

¹³⁵ *Watt v. Alaska*, 451 U.S. 259, 267 (1981).

¹³⁶ *Watt*, 451 U.S. at 266.

¹³⁷ *Posadas v. National City Bank*, 296 U.S. 497, 503 (1936).

¹³⁸ *Rodriguez v. United States*, 480 U.S. 522, 524 (1987) (citations omitted); *see also* *Morton v. Mancari*, 417 U.S. 535, 550-51 (1974).

In a case that is roughly analogous to the current inquiry regarding the interaction of a guidance document and the FCA, a federal court's decision in the FCA *qui tam* suit *United States ex rel. R.C. Taylor III v. Mario Gabelli* may be instructive.¹³⁹ In that case, the defendants argued that a remedial scheme promulgated by the Federal Communications Commission (FCC) for violations of the agency's regulations preempted the FCA and therefore the whistleblower could not apply the FCA to false statements made to the agency.¹⁴⁰ The court noted that repeals by implication are disfavored, but that more detailed statutes may indicate Congress's intent to override more general ones in the area of federal claims and statutory remedies.¹⁴¹ The court further explained that

courts have been 'reluctant to find pre-emption of the [FCA] even where other laws provided closely related regulation and remedies.'¹⁴² Indeed, the legislative history indicates that Congress specifically contemplated the use of the Act to address regulatory violations.¹⁴³

The court found that the defendants did not show, from the legislative history or otherwise, that Congress meant to override the remedies available in the FCA when Congress delegated its authority to create a remedial scheme to the FCC.¹⁴⁴

The court also examined whether the FCC's more specific remedial scheme would preempt the FCA because the agency's remedies were more detailed than those in the FCA.¹⁴⁵ It held that the FCC regulations and the FCA were not in conflict, even if the FCC remedial scheme offered a more detailed remedy than the FCA.¹⁴⁶ Therefore, the court concluded that Congress did not intend "to preclude FCA claims by authorizing the FCC to grant relief for violations of FCC regulations."¹⁴⁷

Assuming that the FDA has the authority to issue guidance on the dissemination of reprints since the expiration of the relevant FDAMA provisions, and that a reviewing court would use reasoning similar to that in *Gabelli*, it appears unlikely that a court would find that Congress intended to preempt the FCA when it delegated general rulemaking authority to the FDA and enacted general statutes relating to guidance issued by the FDA, which the FDA then used to issue its guidance. Whistleblowers in *qui tam* cases have used the FCA to address false claims that stem from regulatory violations of misbranding, and, as the court noted above, the FCA's legislative history shows that Congress had contemplated using the FCA this way.¹⁴⁸ Additionally, as a court noted in a case specifically relating to the dissemination provisions under FDAMA, "the FDA's

¹³⁹ *United States ex rel. R.C. Taylor III v. Mario Gabelli*, 345 F. Supp. 2d 313, 333 (S.D.N.Y. 2004)

¹⁴⁰ *Id.* at 332. The court noted its use of the term "preempt" was atypical because the term preemption does not generally involve two federal laws, but rather a federal law and a state law. *Id.* at 333 n. 112.

¹⁴¹ *Id.* at 333-34 (quoting *United States ex rel. Fallon v. Accudyne Corp.*, 880 F. Supp. 636, 639 (W.D. Wis. 1995)).

¹⁴² *Id.* at 334 (quoting *United States ex rel. Fallon v. Accudyne Corp.*, 880 F. Supp. 636, 639 (W.D. Wis. 1995)).

¹⁴³ *Id.*

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ *Id.*

¹⁴⁷ *Id.* at 334-35.

¹⁴⁸ *Id.* at 334 n.121 (quoting S. Rep. No. 99-345, *reprinted in* 1986 U.S. Code Cong. and Admin. News at 5274: "A false claim [under the act] may take many forms, the most common being a claim for goods or services not provided, or provided in violation of ... statute[] or regulation.").

prosecutorial power flows from its long established authority to prosecute manufacturers for misbranding, *not* from the newly created [now expired] FDAMA” provisions.¹⁴⁹

Therefore, while the FDA’s guidance may indicate how the agency intends to wield its enforcement powers with respect to pharmaceutical manufacturers—because it provides them with the FDA’s “current views and recommendations” regarding dissemination of reprints regarding off-label uses—the agency itself has stated that the “*FDA’s legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved ‘new use’ or whether such activities cause a product to violate the [FFDCA] has not changed.*”¹⁵⁰ This comment echoes the position taken by the FDA in a *Federal Register* notice,¹⁵¹ in which the agency indicated that it could determine a manufacturer’s intent on a case-by-case enforcement basis using its longstanding statutory authorities.¹⁵² Nor would the FDA’s guidance affect the legal authority, enforcement powers, or other capabilities of outside agencies that have been involved in prosecuting FCA cases related to off-label marketing, such as the HHS Office of Inspector General, the Federal Bureau of Investigation, and the Department of Justice.¹⁵³

With regard to cases brought under statutory provisions of the FFDCA, under the guidance, the FDA’s ability to use dissemination of materials regarding off-label or new uses of a drug as evidence in establishing the manufacturer’s intent that the drug be used for a new, unapproved use would not appear to change, either. The FDA could still proceed on a case-by-case basis, using the guidance as a safe harbor for manufacturers who follow it: “if a manufacturer follows the recommendations described ... FDA does not intend to consider the distribution of such medical and scientific information ... as establishing intent that the product be used for an unapproved new use,” which would result in a product being misbranded.¹⁵⁴ But if a manufacturer unlawfully promoted a drug, it appears that dissemination of materials regarding off-label use could be used as evidence of intent and could lead to an enforcement action.¹⁵⁵ The guidance also appears to indicate that unlawful promotion of a drug would invalidate a case where the manufacturer followed the guidance recommendations but illegally promoted a drug. Furthermore, even if the manufacturer’s promotion of an off-label use of a drug fell within the safe harbor of the FDA guidance document, FCA suits may still arise. The off-label use of the drug may still not be covered for reimbursement under federal programs such as Medicaid because the off-label use of the drug would not be for a medically accepted indication (i.e. an FDA-approved use or an off-label use included in a specified drug compendia).¹⁵⁶

¹⁴⁹ *Washington Legal Foundation v. Henney*, 128 F. Supp. 2d 11, 13 (D.C. Cir. 2000).

¹⁵⁰ Guidance Notice, *supra* note 1 (emphasis added); Guidance, *supra* note 3.

¹⁵¹ “If section 401 did not exist, the government could use such dissemination [of materials regarding the off-label or “new use” of a drug] as evidence in establishing a manufacturer’s illegal distribution of a new drug for a “new use,” and in establishing that the product is misbranded.” FDA, Notice: Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14286, 14287 (Mar. 16, 2000).

¹⁵² *Id.* at 14286. The FDA states that, at oral argument in the case, “[p]laintiff Washington Legal Foundation (WLF) expressly agreed that FDA may proceed on a case-by-case basis under pre-FDAMA enforcement authority.” *Id.* at 14287.

¹⁵³ Guidance Notice, *supra* note 1.

¹⁵⁴ Guidance, *supra* note 3.

¹⁵⁵ *Id.*

¹⁵⁶ See text accompanying note 105; see also Medicaid drug coverage provisions at 42 U.S.C. § 1396r-8(K), including coverage for off-label drugs listed in specified compendia at 42 U.S.C. § 1396r-8(g)(1)(B)(i).

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