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Chasing Technology: A Call for FDA Regulation of Pharmaceutical Internet Marketing

Crystal Richardson*

A couple holding hands while lounging in bathtubs, animated bees discussing allergy relief, women looking younger and more beautiful as a result of cosmetic magic: all of these images are frequently associated with the many benefits of pharmaceutical drugs due to active direct-to-consumer (“DTC”) marketing.¹ Pharmaceutical manufacturers traditionally utilized physician education and newspaper or magazine advertisements to market their products, but manufacturers are increasingly using television commercials and Internet advertising as a way to directly inform potential customers about the benefits and risks of their products.² As technology, methods of advertising, and social media continue to advance at a breakneck pace, new forms of advertising inevitably emerge as new technology developments.³ Soon, “tweets” and

* J.D. Candidate, Suffolk University Law School, 2012; B.A., *cum laude*, Mount Holyoke College, 2005. Ms. Richardson may be contacted at clrichardson@suffolk.edu.

¹ See Stuart Elliott, *For Impotence Drugs, Less Wink-Wink*, N.Y. TIMES (Jan. 10, 2006), <http://www.nytimes.com/2006/01/10/business/media/10adco.html> (discussing advertising of Cialis showing man and woman holding hands while soaking in tubs); *Pharmaceutical Advertising Turns to Campaigns Dense With Symbols to Drive Memorable Advertising for the 2006-2007 TV Season*, DRUGS.COM (Oct. 23, 2007), <http://www.drugs.com/news/pharmaceutical-advertising-turns-campaigns-dense-symbols-drive-memorable-advertising-2006-2007-tv-7088.html> (evaluating the success of current pharmaceutical drug ad campaigns); Meredith B. Rosenthal et al., *Promotion of Prescription Drugs to Consumers*, 346 NEW ENG. J. MED. 498, 503-04 (2002) (discussing the impact of increased direct-to-consumer marketing on consumers). Eighty percent of people surveyed had “seen an advertisement for a prescription drug,” indicating “a general awareness of advertising for prescription drugs.” See Rosenthal et al., *supra* note 1, at 504.

² See Alan F. Holmer, *Direct-to-Consumer Advertising – Strengthening Our Health Care System*, 346 NEW ENG. J. MED. 526, 527 (2002) (noting that most direct-to-consumer marketing has traditionally focused on newspapers and magazines); Rosenthal et al., *supra* note 1, at 500-01 (chronicling industry wide trends in direct-to-consumer pharmaceutical promotion). The increasing accessibility of medical information on the Internet motivates pharmaceutical manufacturers to expand their advertising from print media to television ad campaigns and Internet advertising. See Rosenthal et al., *supra*, note 1 at 503.

³ See generally Matthew Scherb, *Free Content’s Future: Advertising, Technology, and Copyright*, 98 NW. U. L. REV. 1787 (2004) (discussing impact of technological changes on advertising). As technology

Facebook advertisements touting the benefits of new pharmaceutical drugs may become as common as the traditional advertisements and commercials that bombard customers.⁴

When pharmaceutical companies started using the Internet to promote their products, the United States Food and Drug Administration (“FDA”) also began monitoring the advertising.⁵ A July 29, 2010 warning letter from the U.S. Federal Food and Drug Administration (“FDA”) commenced the first enforcement action against a pharmaceutical manufacturer for using social media advertising to promote its product.⁶

advances, consumers have much more interactivity with advertising and can control the content of that advertising. *Id.*

⁴ See Christine B. Williams & Girish J. Gulati, *Communicating with Constituents in 140 Characters or Less: Twitter and the Diffusion of Technology Innovation in the United States Congress* (Bentley Univ. Working Paper Series, 2010), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1628247. The number of people using both Facebook and Twitter drastically increased in 2009. *Id.* at 2. Facebook usage increased 105% and Twitter usage increased by 18 million or 900%. *Id.* By the end of February 2012, Twitter’s estimated reach in the United States was over 92 million people per month. *Graph of Estimated US Twitter.com visitors per month*, QUANTCAST.COM, <http://www.quantcast.com/twitter.com> (last updated Mar. 1, 2012).

⁵ Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools, 74 Fed. Reg. 48,083 (Sept. 21, 2009). The FDA needs to address Internet advertising of pharmaceutical drugs because “the Internet has become a widely used medium for companies, including manufacturers, packers, or distributors of medical products regulated by FDA, to disseminate information about their products.” *Id.* at 48,804. The FDA is concerned about how to apply existing regulations, designed to address different advertising mediums, to the Internet due to “[t]he continually evolving nature of the Internet, including Web 2.0 and social media tools, as well as their expansion to applications such as mobile technology.” *Id.* The agency first addressed the issue of Internet regulation in 1996 but failed to issue any guidance documents. Promotion of FDA-Regulated Medical Products on the Internet, 61 Fed. Reg. 48,707 (Sept. 16, 1996) (evaluating how FDA provisions should be applied to internet related materials). As recently as 2009, the FDA issued a Guidance addressing drug and medical device promotion but only mentioned the Internet in a footnote describing promotion communications. See FOOD AND DRUG ADMIN., U.S. DEP’T. HEALTH AND HUMAN SERV., GUIDANCE FOR INDUSTRY PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION, n.9 (2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>. The FDA used the terms “promotional piece, promotional materials, and promotional communications” to refer to “television ads, brochures, booklets, detailing pieces, Internet web sites, print ads, exhibits, and sound recordings or radio ads.” *Id.*

⁶ Warning Letter from the U.S. Food and Drug Administration to Novartis Pharmaceutical Corporation (July 29, 2010) (on file with the Food and Drug Administration), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersToPharmaceuticalCompanies/UCM221325.pdf>. The FDA cited Novartis Pharmaceutical Corporation for having a “Facebook Share” social media widget on their website for the drug Tasigna that generates manufacturer

The letter followed the FDA's November 2009 public hearings on the use of social media in pharmaceutical advertising, demonstrating the most recent step in the slowly developing response to the pharmaceutical companies product advertising and marketing through social media.⁷ Despite the millions of people using social media every day, the FDA has yet to issue any formalized rules detailing what pharmaceutical companies are and are not permitted to do.⁸ Until the FDA promulgates formal rules

created content but fails to cite any of the relevant risks required by the FDA approved labeling of the drug. *Id.* at 1. The FDA explained that

Facebook Share is a way for users of Facebook to share articles, pages, video, or flash content of a site with other Facebook users. Over two billion pieces of content are shared each week through Facebook. With two clicks, visitors to a website can share any page of that website through Facebook by generating a link to the page, along with a thumbnail image and a brief description (i.e., "shared content") that will appear on the users' profiles and, depending on privacy settings, in the home page stream of all of the users' friends. Each time a link is shared by one user, potentially hundreds of new people may see and/or click through on the link.

Id. at n.1. The advertising omits the risks associated with the drug, misleadingly broadens the indication for the drug, overstates the efficacy of the drug, and makes unsubstantiated claims that the drug is superior to others. *Id.* at 2-4. Additionally, the company failed to submit the advertisement to the FDA for approval prior to the dissemination of the information. *Id.* at 5.

⁷ Areta Kupchyk & Kevin Madagan, *Coming Soon! FDA's Current Thinking on Social Media and Product Promotion*, CORPORATE COMPLIANCE INSIGHTS (June 7, 2010), <http://www.corporatecomplianceinsights.com/2010/fda-policy-social-media-product-promotion/> (noting concern over lack of FDA guidance on social media use without violating FDA's "off-label" marketing policies). The FDA held a public hearing in November 2009, soliciting input from the public regarding the new uses of social media. *Id.* Although companies are interested in using new social media because it allows fast and efficient access to consumers, they are also limiting their pharmaceutical advertising because it is not clear exactly what constitutes a violation of FDA regulations. *Id.* Specifically, manufacturers are worried that "any off-label discussion or reference on an interactive social media site will impute knowledge and consent of an unapproved use to the manufacturer." *Id.* The FDA has yet to issue any regulations or formal guidelines that would assist companies in tailoring their marketing campaigns to comply with FDA requirements. See Kellie B. Combs, *FDA Social Media Warning Letter: A Fragmented Approach to a Comprehensive Problem*, 19 WASH. LEGAL FOUND. 1, 2 (2010), available at http://www.wlf.org/Upload/legalstudies/legalopinionletter/10-29-10CombsLegal_Opinion_Letter.pdf.

⁸ See U.S. FOOD AND DRUG ADMIN., GUIDANCE AGENDA: NEW & REVISED DRAFT GUIDANCES CDER IS PLANNING TO PUBLISH DURING CALENDAR YEAR 2011, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm079647.pdf>. The FDA plans on formally publishing a Level 1 guidance but will not commit to a timeframe for publication. See Letter from Thomas Abrams, Director, Division of Drug Marketing, Advertising, and Communications, to Fabio Gratton, Questions for the FDA Regarding "Next Steps" for Guidance Related to the Promotion of FDA-Regulated Medical

addressing pharmaceutical advertising on the Internet, pharmaceutical manufacturers are left in the dark about the FDA's expectations.⁹ Companies can only guess what types of marketing the FDA will consider to be the most responsible way to take advantage of the new technology while still complying with the current regulatory scheme.¹⁰

Part I of this note describes notice-and-comment requirements for agency rulemaking under the Administrative Procedure Act ("APA"). Part II tracks the evolution of FDA regulation of pharmaceutical products, leading to FDA regulation of Internet marketing. Part III describes the current regulatory structure. Part IV highlights recent FDA regulation of pharmaceutical marketing with social media, and Part V argues that the FDA should issue a legislative ruling about the use of social media for pharmaceutical advertising rather than continue with prosecutions. This note concludes by explaining that, until the FDA issues binding regulations setting forth the agency's policies and explanations regarding the use of social media to promote FDA-regulated drugs and medical devices, pharmaceutical manufacturers must continue to promote their products subject to current regulations, which are unclear at best.

I. Notice-and-Comment Requirements for Agency Rulemaking

In general, Congress promotes broad public policy mandates when passing statutes, leaving the agencies to create more detailed regulations through rulemaking.¹¹

Products Using the Internet and Social Media Tools (Dec. 11, 2009) (on file with FDASM), available at [http://www.fdasm.com/docs/FINAL%20DDMAC%20Responses%20to%20FDA SM_Questions.pdf](http://www.fdasm.com/docs/FINAL%20DDMAC%20Responses%20to%20FDA%20SM_Questions.pdf); see also Kupchyk & Madagan, *supra* note 7 (discussing FDA's emerging social media policy).

⁹ See *supra* notes 7-8 and accompanying text.

¹⁰ See Kupchyk & Madagan, *supra* note 7. In order to determine how the FDA will interpret Internet advertising, pharmaceutical manufacturers must rely on individual enforcement actions. *Id.* All enforcement actions have been based on the current regulatory structure, designed for more traditional mediums, such as television commercials and print advertising, because the FDA has not issued a guidance document addressing social media. *Id.*

¹¹ See Michael Kolber, *Rulemaking Without Rules: An Empirical Study of Direct Final Rulemaking*, 72 ALB. L. REV. 79, 83-84 (2009) (analyzing the successes and failures of notice-and-comment rulemaking procedures). When Congress enacted the APA, industries such as transportation, consumer products, and communications had become so large and complex that it was impracticable for Congress to address separately and directly. *Id.* at 84. Therefore, Congress created agencies and delegated to them the authority to pass rules enforcing the general public policy. *Id.* See also Erica Seiguer & John J. Smith, *Perception and Process at the Food and Drug Administration: Obligations and Trade-offs in Rules and Guidances*, 60 FOOD & DRUG L.J. 17, 18 (2005) (describing background of rules and guidelines). Agency rules "may interpret and/or implement a statute." *Id.*

As an administrative agency, the FDA is a source of rulemaking authority and must comply with the minimum requirements imposed by the Administrative Procedure Act (“APA”) when issuing rules that bind the public.¹² When Congress passed the Food, Drug and Cosmetic Act of 1938 (“FDCA”), it delegated power to the FDA to protect the public from drugs that have not been proven to be safe or effective.¹³ Congress delegated the FDA with the authority to issue regulations because it was impracticable to expect legislators to have the requisite knowledge and level of scientific expertise to successfully address the various issues pertaining to food and drug testing and regulation.¹⁴ The APA requires that every agency promulgate rules using notice-and-

¹² See Administrative Procedure Act, Pub. L. No. 79-404, 60 Stat. 237 (1946) (codified as amended in scattered sections of 5 U.S.C.). All agencies, including the FDA, must comply with the “rulemaking” procedure outlined by Congress. *Id.* § 553(a). The FDA is an agency under the Department of Health and Human Services, comprised of six Centers: Center for Drug Evaluation and Research (“CDER”), Center for Biologics Evaluation and Research (“CBER”), Center for Devices and Radiological Health (“CDRH”), Center for Food Safety and Applied Nutrition (“CFSAN”), Center for Veterinary Medicine (“CVM”), and Center for Tobacco Products (“CTP”). *Centers & Offices*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/default.htm> (last visited Jan. 20, 2012). Combination products are evaluated through the Office of Combination Products (OCP), established in 2002 and located in the Office of the Commissioner (OC). *Office of Combination Products*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018184.htm> (last updated Oct. 21, 2011).

¹³ Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. §§ 301-399 (2006). Congress enacted the FDCA to protect the public by securing the purity of food and drugs and informing purchasers of what they are buying. See *id.* § 342(b) (preventing the introduction of “adulterated” or “misbranded” into interstate commerce); *United States v. Two Bags, Each Containing 110 Pounds, Poppy Seeds, et al.*, 147 F.2d 123, 126 (6th Cir. 1945) (explaining that the FDCA “was intended to protect the public against adulteration of articles of food by the addition of substances deleterious to the health of consumers.”). The FDA’s mission is:

protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation . . . FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

What We Do, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/default.htm> (last visited Jan. 17, 2012).

¹⁴ See John P. Swann, *How Chemists Pushed For Consumer Protection – The Food and Drugs Act of 1906*, 24 CHEMICAL HERITAGE 2 (2006), available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/Chemistsandthe1906Act/ucm126648.htm> (chronicling influential chemists who helped steer the FDA into existence). Harvey Washington Wiley, the fourth chemist to head the predecessor agency to the FDA, tested tainted food and focused on

comment procedures, and the FDA has created self-imposed additional procedural requirements for passing new non-legally binding guidelines.¹⁵ Taken together, these requirements shape the FDA's exercise of its rulemaking power.¹⁶

Much of the FDA's regulatory power, including its ability to regulate off-label drug marketing, stems from its informal rulemaking authority.¹⁷ The APA defines a rule as "the whole or part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency."¹⁸ This includes non-binding rules and policy statements, such as guidance documents, intended to establish best practices for agencies.¹⁹ All informal rules must undergo the notice-and-

commonly used food preservatives. *Id.* His technical knowledge about food contamination helped to justify passing a comprehensive food and drug bill to protect the public. *Id.*

¹⁵ Administrative Procedure Act, 5 U.S.C. § 553(b) (2006) (outlining notice and comment procedures required for administrative rulemaking to be legally enforceable); 21 C.F.R. § 10.115 (2011) (detailing the FDA good guidance practices). An agency does not have to adhere to the notice-and-comment procedure if it is merely issuing "interpretive rules, general statements of policy or rules of agency organization, procedure or practice." 5 U.S.C. § 553(b)(3)(A) (2006). The FDA has created their own self-governing rules for passing guidance documents, known as "good guidance practices." 21 C.F.R. § 10.115(a) (2011). When promulgating guidance documents, the FDA must give notice of the proposed guidance documents and give the public a chance to comment on the proposed regulatory statement. *Id.* § 10.115(g).

¹⁶ See Seiguer & Smith, *supra* note 11, at 18 (discussing the ways in which the FDA communicates their regulatory expectations to the public). The FDA puts pharmaceutical manufacturers and the general public on notice of their opinions through rules and guidance documents. *Id.* The different types of statements have different legal effects: "rules may interpret and/or implement a statute, whereas a guidance explains FDA's current thinking on a particular issue." *Id.*

¹⁷ See Seiguer & Smith, *supra* note 11, at 23 (discussing reasons why the FDA may prefer to issue guidance documents over rules). Guidance documents can be passed faster than rules, and therefore can address scientific and technological issues that develop rapidly. *Id.*

¹⁸ 5 U.S.C. § 551(4) (2006) (stating "rules" are either "legislative rules," which create new laws, rights or duties, or "interpretive rules," which clarify existing statutes or regulations); *Clarry v. United States*, 85 F.3d 1041, 1048 (2nd Cir. 1996) (holding that a policy was an interpretive rule because it did not create new rights). Rules have three distinct elements: "the whole or part of an agency statement," "general or particular applicability and future effect," and they must be "designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency." 5 U.S.C. § 551(4) (2006); *Abs v. Sullivan*, 756 F. Supp. 1172, 1187 (W.D. Wis. 1990) (outlining elements required for "rule").

¹⁹ See *Abs*, 756 F. Supp. at 1187 (finding an agency guideline to be an agency rule because the guideline included each of the elements required for a "rule"). Whether or not an agency statement is a "rule" under the APA turns on the binding impact, not the title of the communication. *Western Coal Traffic League v. United States*, 694 F.2d 378, 392 (5th Cir. 1982) (finding that even though the commission titled the statements as "guidelines" and not "rules," they were "rules" as defined under the APA). Even if something is titled a "guideline," the court

comment process unless the agency is attempting to promulgate “interpretive rules, general statements of policy, or rules of agency organization, procedure or practice.”²⁰

When passing a rule, the APA notice-and-comment process requires an agency to give notice of a proposed rule, accept and respond to public comments in the final rule, and state the legal basis and purpose behind the rule.²¹ Once the finalized rule is published in the *Federal Register*, it is codified in the *Code of Federal Regulations*.²² Notice-and-comment rulemaking exists to allow for public participation and input into the formal rulemaking process.²³ Public participation “increases accountability and

must look to see if the document includes binding language such as “obligations” and “will.” *Id.* If such language is present, the nomenclature will have no impact and the “guideline” should be deemed to be a “rule.” *Id.*

²⁰ Administrative Procedure Act, 5 U.S.C. § 553(b)(3)(A) (2006). Statements by agencies that do not create new laws, rights, or duties are exempt from notice-and-comment requirements simply because they do not create new substantive rights. *Clarry*, 85 F.3d at 1048 (finding labor policy deeming strikers ineligible for reemployment did not create or change any existing law, right, or duty and was exempt from notice-and-comment procedural requirements). However, the exemptions to the notice-and-comment requirements are meant to be narrowly construed. *See Wells v. Schweiker*, 536 F. Supp. 1314, 1324 (E.D. La. 1982).

²¹ *See* 5 U.S.C. § 553 (2006) (requiring publication and public comments when promulgating new agency rules). The agency must give general notice of the proposed rule in the *Federal Register*. *Id.* § 553(b). The notice must include “(1) a statement of the time, place, and nature of public rule making proceedings; (2) reference to the legal authority under which the rule is proposed; and (3) either the terms or substance of the proposed rule or a description of the subjects and issues involved.” *Id.* § 553(b)(1)-(3). After putting the public on notice of the proposed rule, the agency must “give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation.” *Id.* § 553(c). At least thirty days notice must be given before publishing the finalized rule. *Id.* § 553(d). Finally, the agency must consider any relevant matter presented in the public comments, and include “a concise general statement of their basis and purpose” in the finalized rule. *Id.* § 553(c).

²² 5 U.S.C. § 553(c) (2006) (requiring agencies to publish their rules in the *Federal Register*); *Seiguer & Smith*, *supra* note 11, at 18 (stating that finalized rules are codified in the *Code of Federal Regulations*).

²³ *See Texaco, Inc. v. Fed. Power Comm’n*, 412 F.2d 740, 744 (3rd Cir. 1969) (stating “section 553 was enacted to give the public an opportunity to participate in the rule-making process”); *Nat’l Retired Teachers Ass’n v. U.S. Postal Serv.*, 430 F. Supp 141, 147 (D.D.C. 1977) (explaining that “[o]ne of the central purposes of the notice and comment requirements is to allow public participation in the promulgation of rules which have a substantial impact on those regulated”). In addition to soliciting the public input and making the entire process more democratic, the procedures allow each agency to become more informed about the particular topic. *Chocolate Mfrs. Ass’n of the U.S. v. Block*, 755 F.2d 1098, 1103 (5th Cir. 1984) (quoting *Natl. Tour Brokers Ass’n v. United States*, 591 F.2d 896, 902 (D.C. Cir. 1978)) (“purpose of the notice-and-comment procedure is both ‘to allow the agency to benefit from the experience and input of the parties

oversight, provides better quality information for both decision makers and participant, minimizes excessive influence of powerful interests, and promotes proceduralist values that enhance fairness and legitimacy of a rule.”²⁴

The FDA, like many other agencies, imposes stricter procedures than those required under the APA when issuing non-binding interpretations of the law.²⁵ The APA exempts interpretive rules and general statements of policy from formal notice-and-comment requirements.²⁶ The FDA self-imposes procedures similar to the notice-and-comment requirements when promulgating its interpretive rules and general statements of policy—both of which are placed under the umbrella of guidance documents.²⁷ FDA guidance documents include “documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue,” but do not include “documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms.”²⁸ The FDA clearly states that the guidance

who file comments . . . and to see to it that the agency maintains a flexible and open-minded attitude towards its own rules”). The expert input helps to educate the agency, “thereby helping to ensure informed agency decision making.” *Id.*

²⁴ Stephanie Stern, *Cognitive Consistency: Theory Maintenance and Administrative Rulemaking*, 63 U. PITT. L. REV. 589, 594 (2002) (discussing benefits of rulemaking that involves public input). Proponents of the notice and comment procedures argue that public involvement creates a broader information base and mediates the relationship between the government and democracy. *Id.* Opponents of public participation argue that soliciting public comments ultimately delays rulemaking and increases administrative costs. *Id.*

²⁵ See Food and Drug Administration (FDA) Modernization Act of 1997, Pub. L. No. 105-115, § 405, 111 Stat. 2296, 2368-69 (1997) (codifying portions of the FDA’s good guidance practices) (“FDAMA”). The FDAMA directed the FDA to issue regulations detailing its “policies and procedures for the development, issuance, and use of guidance documents.” *Id.*

²⁶ See Seiguer & Smith, *supra* note 11, at 18.

²⁷ See *supra* notes 18-19 and accompanying text; see also Seiguer & Smith, *supra* note 11, at 20. Even though the FDA does not have to promulgate guidance documents with the same formal notice-and-comment procedure, the FDA’s Good Guidance Practices require similar public notice. See Seiguer & Smith, *supra* note 11, at 20.

²⁸ 21 C.F.R. § 10.115(b)(1)-(3) (2011). Each guidance document must:

- (i) Include the term “guidance,”
- (ii) Identify the center(s) or office(s) issuing the document,
- (iii) Identify the activity to which and the people to whom the document applies,
- (iv) Prominently display a statement of the document’s nonbinding effect,
- (v) Include the date of issuance,
- (vi) Note if it is a revision to a previously issued guidance and identify the document that it replaces, and

documents are not legally binding, but functionally the pharmaceutical industry often views guidelines as though they are rules.²⁹

Guidance documents are subject to two different levels of public input based on the nature of the document: Level 1 guidance documents require notice-and-comment procedures; whereas Level 2 guidance documents do not.³⁰ Level 1 documents “(i) set forth initial interpretations of statutory or regulatory requirements; (ii) set forth changes in interpretation or policy that are of more than a minor nature; (iii) include complex scientific issues; or (iv) cover highly controversial issues.”³¹ For Level 1 guidance documents, the FDA must publish a notice of the proposed guidance in the *Federal Register* and invite public comment, mirroring the ADA notice-and-comment requirements.³² After a Level 1 guidance document has been finalized, the public is free to continue submitting comments, which may be considered if the FDA chooses to revise the guidance document in the future.³³ In comparison, all guidance documents that are not Level 1 documents are Level 2; Level 2 guidance documents typically address established agency practices or set forth minor changes in interpretation or policy.³⁴ Level 2 guidance documents are implemented as soon as the FDA publishes

(vii) Contain the word “draft” if the document is a draft guidance.

Id. § 10.115(i)(1)(i)-(vii). Guidance documents cannot use “mandatory language such as ‘shall,’ ‘must,’ ‘required,’ or ‘requirement,’ unless FDA is using these words to describe a statutory or regulatory requirement.” *Id.* § 10.115(i)(2).

²⁹ *See id.* § 10.115(d) (responding to question “Are you or FDA required to follow a guidance document?”). Even though the FDA states that guidance documents “do not create legally enforceable rights and responsibilities,” they bind themselves and their agents by allowing deviation from the guidance documents “only with appropriate justification and supervisory concurrence.” *Id.* § 10.115(d)(1)-(3). However, industry representatives feel that guidance documents are enforced as though they are legally binding. *See* Seiguer & Smith, *supra* note 11, at 29-30 (reporting results of interviews with FDA and pharmaceutical industry representatives).

³⁰ *See* 21 C.F.R. § 10.115(c) (2011) (dividing guidance documents into Level 1 and Level 2 guidance documents). The FDA established different procedures for promulgating Level 1 and Level 2 guidance documents. *See id.* § 10.115(g). The FDA must solicit public input when issuing a Level 1 guidance but does not have to give any notice before issuing Level 2 guidance. *Id.*

³¹ *Id.* § 10.115(c)(1)(i)-(iv).

³² *Id.* § 10.115(g)(1)-(3).

³³ *Id.* § 10.115(f)(3)-(4). The public is free to “submit drafts of proposed guidance documents for FDA to consider” at any time. *Id.* § 10.115(f)(3). Furthermore, the public “can, at any time, suggest that FDA revise or withdraw an already existing guidance document.” *Id.* § 10.115(f)(4). Suggestions “should address why the guidance document should be revised or withdrawn and, if applicable, how it should be revised.” *Id.*

³⁴ *Id.* § 10.115(c)(2).

and posts the document to the Internet.³⁵ Like Level 1 guidance documents, the public may submit comments following publication, and the FDA reserves the right to revise the documents when appropriate.³⁶

The FDA has the discretion to choose whether to issue a rule or a guidance document.³⁷ Occasionally the FDA must enact a rule, but only under limited circumstances, such as when Congress enacts a statute directing the agency to issue a rule, or when an existing rule must be revoked or amended.³⁸ If the FDA needs the decision to be legally binding on the entire industry, they must issue a rule because guidance documents by definition are not legally enforceable.³⁹ If they must respond rapidly to a quickly evolving situation, however, guidance documents may be more appropriate, as they are not subject to the strict notice-and-comment procedures that must precede the enactment of new regulations.⁴⁰ Guidance documents also offer more flexibility than rules because they are amendable.⁴¹

³⁵ *Id.* § 10.115(g)(4)(i)(A)-(B). When issuing Level 2 guidance, the FDA will: “(A) Post the guidance document on the Internet and make it available in hard copy; (B) Immediately implement the guidance document, unless FDA indicates otherwise when the document is made available; and (C) Invite your comment on the Level 2 guidance document.” *Id.* § 10.115(g)(4)(i)(A)-(C).

³⁶ 21 C.F.R. §§ 10.115(g)(4)(i)(C), (g)(4)(ii) (2011).

³⁷ Seiguer & Smith, *supra* note 11, at 22 (discussing who has the discretion over the decision whether to enact a rule or promulgate a guidance document). When making the decision, the FDA should consider whether or not they desire legal enforceability and the resulting impact on the food and drug industry and the medical community. *Id.* They should also seek to successfully and expeditiously translate scientific and technological advances into better consumer health products and advance public health generally. *Id.*

³⁸ See Administrative Procedure Act, 5 U.S.C. § 551(4) (2006) (defining “rule”). If an agency must “implement . . . law or policy,” they are limited to passing a rule. *Id.* Additionally, only rules can “interpret, or prescribe law or policy.” *Id.* Rules must include, but are not limited to: “the approval or prescription for the future of rates, wages, corporate or financial structures or reorganizations thereof, prices, facilities, appliances, services or allowances therefore or of valuations, costs, or accounting, or practices bearing on any of the foregoing.” *Id.*

³⁹ See *supra* note 29 and accompanying text (discussing the legal enforceability of guidance documents).

⁴⁰ See Seiguer & Smith, *supra* note 11, at 22 (reviewing advantages and disadvantages of rules and guidelines). The FDA desires flexibility in situations where science or technology may be advancing at such a rapid pace that it is not practicable to bind anyone to bright line rules. *Id.* Occasionally agencies must have the ability to pass rules more quickly, such as when responding to medical emergencies, and additional resources will be applied so that the rule can be swiftly published. *Id.*

⁴¹ See Seiguer & Smith, *supra* note 11, at 22 (discussing benefits of guidance documents). If science and technology are advancing at rapid speeds, both the FDA and those regulated benefit from flexibility in the regulatory policy. *Id.*

II. The History of the FDA's Role as Regulator of Pharmaceutical Marketing

The FDA currently holds broad power to regulate food, drugs, medical devices, and cosmetics, but the agency has not always had such expansive regulatory power.⁴² Prior to 1906, pharmaceutical products were largely unregulated, and virtually anyone could sell any concoction claiming to cure or prevent ailments.⁴³ The Pure Food and

⁴² Federal Food, Drug, and Cosmetics Act 21 U.S.C.A. § 321(f), (g)(i), (h), (i) (2009) (defining the products that the FDA regulates). “Food” is defined as “articles used for food or drink for man or other animals, chewing gum and articles used for components of any such article.” *Id.* § 321(f). “Drugs” include:

(A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Id. § 321(g)(1). Congress defines “devices” as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--(1) recognized in the official National Formulary, or the United States Pharmacopœia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Id. § 321(h). “Cosmetics” is defined as:

articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and articles intended for use as a component of any such articles; except that such term shall not include soap.

Id. § 321(i). See John P. Swann, *FDA's Origin*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm> (last updated June 18, 2009) (describing the FDA as growing from a single chemist working for the USDA to a department that employs 9,100 people and operates on a \$1.29 billion budget).

⁴³ Katherine A. Helm, *Protecting the Public Health from Outside the Physician's Office: A Century of FDA*

Drug Act of 1906 granted the Department of Agriculture's Bureau of Chemistry, a precursor to the FDA, the power to regulate drugs.⁴⁴ The act made introducing "adulterated" or "misbranded" drugs into interstate commerce a federal offense.⁴⁵ Drugs differing in strength, quality, or purity from the professional standard were generally considered adulterated.⁴⁶ A drug was misbranded if the manufacturer sold it under a different name, did not label the drug with the correct quantity or proportion, or made false or misleading claims regarding the therapeutic effects.⁴⁷ The Act did not

Regulation from Drug Safety Labeling to Off-Label Drug Promotion, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 125 (2007) (describing the regulatory climate in the late nineteenth century). No federal regulatory structure existed to evaluate pharmaceutical product to ensure their safety or efficacy before entering the market or to substantiate the claims their producers made in advertisements. Victor E. Schwartz et al., *Marketing Pharmaceutical Products in the Twenty-First Century: An Analysis of the Continued Viability of Traditional Marketing Principles of Law in the Age of Direct-to-Consumer Marketing*, 32 HARV. J.L. & PUB. POL'Y 333, 337 (2009). The traveling salesman hawking cure-alls, elixirs and snake oils, a character found in the mythology of the American West, stems from this unregulated period. *Id.*

⁴⁴ Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, ch. 3915, 34 Stat. 768 (1906) (codified as amended at 21 U.S.C. §§ 1-15 (1906)), *repealed by* Federal Food, Drug, and Cosmetic Act, ch. 675, § 902(a), 52 Stat. 1040, 1059 (1938). Congress passed the law in response to the deplorable conditions described in Upton Sinclair's *The Jungle*. See generally Upton Sinclair, *THE JUNGLE* (1905); see also Michael I. Krauss, *Loosening the FDA's Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare*, 4 GEO. MASON L. REV. 457, 459 (1996) (chronicling the origins of the FDA's "Certification Monopoly").

⁴⁵ Federal Food and Drugs Act of 1906, 21 U.S.C. § 2 (repealed 1938). Specifically, Congress prohibited "the introduction into any State or Territory or the District of Columbia from any other State or Territory or the District of Columbia, or from any foreign country, or shipment to any foreign country of any article of food or drugs which is adulterated or misbranded." *Id.*

⁴⁶ *Id.* § 7. The Federal Food and Drugs Act of 1906 deemed drugs to be "adulterated":

when a drug is sold under or by a name recognized in the United States Pharmacopoeia or National Formulary, it differs from the standard of strength, quality, or purity, as determined by the test laid down in the United States Pharmacopoeia or National Formulary official at the time of investigation. No drug defined in the United States Pharmacopoeia or National Formulary shall be deemed to be adulterated under this provision if the standard of strength, quality, or purity be plainly stated upon the bottle, box, or other container thereof although the standard may differ from that determined by the test laid down in the United States Pharmacopoeia or National Formulary.

Id.

⁴⁷ *Id.* § 8. The Federal Food and Drugs Act of 1906 applied the term "misbranded" to: all drugs, or articles of food, or articles which enter into the composition of food, the package or label of which shall bear any statement, design, or device

distinguish between drugs requiring a prescription and drugs sold directly to the consumer (“over-the-counter”).⁴⁸ Although the Pure Food and Drug Act of 1906 subjected the pharmaceutical industry to federal regulation, only labeling fraud was a federal crime.⁴⁹ Thus, drug manufacturers determined how to promote and market their drugs subject only to state law.⁵⁰

The Pure Food and Drug Act of 1906 put the public on notice of the contents of commercially available pharmaceutical products by requiring manufacturers to label their products; it did not, however, address the safety or efficacy of the drugs.⁵¹ In the pro-business economic climate of the 1920s, the Bureau of Chemistry did not actively exercise its regulatory authority, and took a relaxed stance towards enforcement of the regulations against pharmaceutical manufacturers.⁵² The permissive approach changed

regarding such article, or the ingredients or substances contained therein which shall be false or misleading in any particular, and to any food or drug product which is falsely branded as to the State, Territory, or country in which it is manufactured or produced.

Id.

⁴⁸ See Krauss, *supra* note 44, at 459 (discussing lack of governmental oversight of drugs and pharmaceuticals at the turn of the nineteenth century); Helm, *supra* note 43, at 125 (describing regulatory conditions under the Federal Food and Drug Act of 1906). Even though many people relied on the advice of physicians, the Act did not require a prescription in order to sell the pharmaceuticals. Krauss, *supra* note 44, at 459. Federal regulations did not determine which drugs would be controlled by the prescription process until 1951. Durham-Humphrey Amendment of 1951, Pub. L. No. 82-215, ch. 578, 65 Stat. 648 (1951) (codified in part at 21 U.S.C. § 353 (2004)).

⁴⁹ See *DeFreese v. United States*, 270 F.2d 730, 733-34 (5th Cir. 1959), *cert. denied*, 362 U.S. 944 (1960) (distinguishing between retail and wholesale sale of drugs without a prescription). Appellants attempted unsuccessfully to align themselves with drug manufacturers who were not required to have a physician prescription before selling drugs wholesale to pharmacies and other retailers. *Id.* See also Swann, *supra* note 42.

⁵⁰ See Swann, *supra* note 14. Before the passage of the Pure Food and Drug Act of 1906, states exercised primary control over domestically produced foods and drugs while federal authority was limited to imported products. *Id.* This led to policy variations from state to state. *Id.*

⁵¹ See *Sherley Amendment of 1912*, ch. 352, 37 Stat. 416 (1912). This amendment was passed in response to the Supreme Court’s ruling that the 1906 Act applied only to false statements made about the identity of the drug (for instance, strength, quality, purity) and not to statements made about the curative effect (for example, effectiveness as a cure for cancer). See *United States v. Johnson*, 221 U.S. 488, 497 (1911).

⁵² Mary T. Griffin, *AIDS Drugs and the Pharmaceutical Industry: A Need for Reform*, 17 AM. J.L. & MED. 363, 376 (1991) (explaining early attempts at policing the pharmaceutical industry). Regulation took the form of negotiations, and the Bureau of Chemistry was accused of colluding with the manufacturers. *Id.* Criminal prosecutors faced challenges when attempting to enforce the Act because the average traveling salesman was difficult to locate. See Krauss, *supra* note 44,

in 1937 when several children died after ingesting a drug that had been tested for flavor but not for safety.⁵³ The public outcry that followed prompted an increase in the regulation of drug manufacturers.⁵⁴ In 1938, President Roosevelt signed the Federal Food, Drug and Cosmetic Act of 1938 (“FDCA”), granting the FDA broad authority to regulate the manufacture, labeling, and promotion of drugs, biological products, and medical devices.⁵⁵

The FDCA effectively cemented the FDA’s role as guardian of public safety and changed the relationship between pharmaceutical manufacturers and the federal government.⁵⁶ For the first time, pharmaceutical manufacturers were required to test all new drugs for safety and submit the results to the FDA for approval before introducing a drug into interstate commerce.⁵⁷ Drugs had to be labeled and could only be marketed

at 460. Additionally, the Bureau bore the burden of proving criminal intent, which is more difficult than proving tortious negligence. *Id.*

⁵³ See David L. Stepp, *The History of FDA Regulation of Biotechnology in the Twentieth Century* 8 (Winter 1999) (unpublished third-year paper, Harvard Law School), available at http://leda.law.harvard.edu/leda/data/257/Stepp,_David_00.pdf (describing events leading to the passage of the Food, Drug and Cosmetics Act of 1938). More than seventy people were poisoned by “Elixir Sulfanilamide” when the manufacturer dissolved the drug, in powder form, in a solvent in order to produce a liquid that was more palatable to children. *Id.* After the product was identified as the cause of the fatalities, it became apparent that basic animal testing or a review of medical literature would have revealed the toxicity. *Id.* Even if the manufacturers had known the product was poisonous, the Pure Food and Drug Act of 1906 still would not have effectively protected the public because the Act did not provide for any clinical safety testing of the drugs and only operated to police products that were already on the market. See *id.* at 8-9.

⁵⁴ See Helm, *supra* note 43, at 126 (chronicling the events leading to the formation of the FDA). Because the FDA’s regulatory reach only extended to labeling, Congress recognized a need for substantive pre-market testing of drugs before they were sold to the public. *Id.*

⁵⁵ Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301-399d (2006)). In 1927, the Bureau of Chemistry was renamed the Food, Drug, and Insecticide Administration. See Swann, *supra* note 42. The name was shortened to the Food and Drug Administration in 1930. *Id.*

⁵⁶ See Helm, *supra* note 43, at 128 (“FDCA created a new healthcare landscape and, effectively, architected the FDA’s role as guardian of public safety in the drug industry”). The regulatory power of the FDA diminished the control the pharmaceutical companies had in the marketplace, because they were no longer free to market their drugs until obtaining FDA approval. *Id.* at 127. Unsurprisingly, the pharmaceutical industry vehemently opposed the FDA-mandated changes, arguing that the required evidence of safety would severely hinder research efforts, delay the introduction of new drugs to the market, and undermine consumers’ freedom to self-medicate. See Griffin, *supra* note 52, at 376.

⁵⁷ Federal Food, Drug, and Cosmetic Act § 505, 52 Stat. at 1052-53. The original FDCA defined a “new drug” as “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 of

after the FDA found the product safe for use and approved the label.⁵⁸ Drug manufacturers initially retained discretion over the classification of their drugs as prescription or over-the-counter.⁵⁹ After several episodes of consumer misuse, Congress amended the FDCA in 1951 to distinguish between drugs that could only be dispensed by a licensed medical practitioner, and those that could be sold over-the-counter.⁶⁰

The FDA began evaluating efficacy in addition to safety when Congress passed the 1962 Kefauver-Harris Amendments, also known as the Drug Efficacy

drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .” *Id.* § 201(p)(1), 52 Stat. at 1041-42. It prohibited the introduction, or delivery for introduction, into interstate commerce of any new drug for which an application had not been submitted to and allowed by FDA to become effective. *Id.* § 505(a), 52 Stat. at 1052. A New Drug Application (“NDA”) consisted of the following:

- (1) full reports of investigations which have been made to show whether or not such drug is safe for use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary [of Agriculture] may require; and (6) specimens of the labeling proposed to be used for such drug.

Id. § 505(b)(1)-(6), 52 Stat. at 1052. If the NDA met the required safety criteria and the FDA took no action to reject the NDA within a fixed period of time after its filing, it became effective and the drug was de facto approved for marketing. *See Hoffman-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890, 892 (D.D.C. 1975) (“Under the original 1938 Act, new drug applications were deemed approved within a fixed period unless the Secretary took affirmative steps to reject the application”).

⁵⁸ *See* Federal Food, Drug, and Cosmetic Act § 505(b)(6), 52 Stat. at 1052 (requiring drug sponsors to submit the labeling for FDA approval as part of an NDA). A drug was deemed “misbranded” and subject to FDA regulation if the label was “false or misleading in any particular.” *Id.* § 502(a), 52 Stat. at 1050. Every label had to contain “the name and place of business of the manufacturer, packer or distributor; and . . . an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.” *Id.* § 502(b), 52 Stat. at 1050.

⁵⁹ *See supra* note 48 and accompanying text.

⁶⁰ Durham-Humphrey Amendment, Pub. L. No. 82-215, 65 Stat. 648 (1951) (amending Federal Food, Drug, and Cosmetic Act §§ 303(c), 503(b)) (codified as amended at 21 U.S.C. § 353 (2006)). The amendment mandated that physicians write prescriptions to dispense drugs that were habit-forming, potentially unsafe or only effective in limited situations. *Id.* Labels for prescription drugs had to contain the statement “Caution: Federal law prohibits dispensing without prescription” to avoid prosecution for misbranding. *Id.* 65 Stat. at 649.

Amendments.⁶¹ In order to meet safety standards, the drug had to be safe for human consumption; to meet efficacy standards, the drug additionally had to treat the specific condition or indication that the manufacturers claimed it would treat.⁶² A European health care crisis prompted Congress to put in place the protectionist system of drug regulation that is currently in place in the United States.⁶³ The Drug Efficacy Amendments forbade the shipment of any new drug in interstate commerce that the FDA had not formally approved for safety and efficacy, and made FDA approval a more stringent and extended process.⁶⁴ The drug's sponsor, typically the pharmaceutical manufacturer, had to get FDA pre-approval for testing a new drug, conduct clinical research trials for each individual use of the drug, and submit the results to the FDA for approval.⁶⁵ This process placed the ultimate responsibility on the drug sponsor to

⁶¹ Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C.). Congress declared that the purpose of the Act was, in part, to "protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs." *Id.* 76 Stat. at 780.

⁶² *Id.* 76 Stat. at 780-81.

⁶³ See Helm, *supra* note 43, at 128-29 (explaining shift in FDA regulatory policy resulting from thalidomide crisis); Joseph G. Contrera, Comment, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 935 (1995) (describing conditions surrounding passage of the Kefauver-Harris Amendments). In Europe, physicians prescribed thalidomide as a sleep aid and to relieve morning sickness in pregnant women. Helm, *supra* note 43, at 128. The drug had not yet been tested for potential toxicology on fetuses, and some children born to women who had taken thalidomide during pregnancy were born with "flipper-like" limbs. Contrera, *supra*, at 935 n.33. The drug was pending approval in the United States when Europeans discovered this devastating side effect, and "fear that such an event would take place in the U.S. spurred Congress to enact more stringent drug regulation laws." Helm, *supra* note 43, at 128-29. For a discussion of similar drug safety issues occurring during this time period on a worldwide scale, see generally Jerry Avorn, *Learning About the Safety of Drugs—A Half-Century of Evolution*, 365 NEW ENG. J. MED. 2151 (2011).

⁶⁴ Kefauver-Harris Amendments § 104, 76 Stat. at 784. Whereas previously an NDA could become de facto approved if not rejected, the FDA now must affirmatively approve all NDAs before the drugs can be introduced into interstate commerce and marketed. *Id.* § 102(c), 76 Stat. at 781. See generally Krauss, *supra* note 44, at 461-62 (explaining origins of FDA certification).

⁶⁵ See Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355 (2006); 21 C.F.R. § 312.22(a) (2011) (outlining general requirements for IND submission). Before new drugs can even be tested for safety or efficacy, drug sponsors must submit an Investigational New Drug Application ("IND") to the FDA. 21 C.F.R. §§ 312.22(a), 312.3(b). The IND must focus on "the general investigational plan and the protocols for specific human studies." *Id.* § 312.22(c). The IND must contain:

an identification of the active and inactive components of the product, manufacturing data, proposed labeling, identification and experience of the principal investigators, a limited environmental impact analysis, putative

provide sufficient evidence that the proposed drug was a safe and effective therapy and had a risk-benefit balance appropriate for use to treat human disease.⁶⁶ All drug safety

therapeutic uses, preferred route of administration, a summary of all pharmacological and toxicological data and testing, and a proposal for a clinical research protocol.

Stepp, *supra* note 53, at 15 (outlining requirements for IND). The FDA and a local Independent Review Board (“IRB”) need to approve the IND before drug manufacturers are permitted to begin the human clinical trials. *See* 21 C.F.R. § 312.2(b) (2011) (exempting clinical investigations from prior FDA approval requirement). Once the FDA grants the pre-approval, the sponsor typically conducts three phases of clinical trials: phase I determines the toxicity of the drug in humans; phase II tests the therapeutic effect in patients with the target illness; and phase III consists of an expanded series of blind clinical trials with a wider range of patients. Stepp, *supra* note 53, at 15-17. After completing the clinical trials, the drug sponsor must submit a NDA containing:

(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title.

Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355(b)(1)(A)-(G).

⁶⁶ *See* 21 U.S.C. § 355(d)(5) (granting the Secretary the power to deny an application if sponsor does not provide “substantial evidence” that the drug is effective). The trials must produce “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” *Id.* Evidence cannot be anecdotal or individual opinion and must consist of:

adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Id. § 355(d). Even though a drug will always be safe for human consumption or not, not every drug will always be perfectly effective for each of its intended uses, so the standard for evaluation is “whether the expected benefits of the new product or use (given by its efficacy to users) outweigh its expected costs (given by its safety risks to users.” Dov Fox, *Safety, Efficacy, and Authenticity: The Gap Between Ethics and Law in FDA Decisionmaking*, 2005 MICH. ST. L. REV. 1135, 1160-61 (2005) (discussing cost-benefit analysis applied to FDA new drug approvals).

and efficacy determinations were comprehensively under the control of the FDA by 1962.⁶⁷

Just as before, the pharmaceutical industry objected to the Drug Efficacy Amendments, arguing they increased costs and created even longer approval times.⁶⁸ In response, the FDA introduced a new process wherein the drug sponsor could file a Supplemental New Drug Application (“SDNA”) for separate FDA approval of each new therapeutic use of a pre-approved pharmaceutical product.⁶⁹ Rather than submitting an Investigational New Drug Application (“IND”) and New Drug Application (“NDA”) every time a new use was discovered, the drug sponsor only had to submit an SDNA if the drug already went through the formal approval process for a different therapy.⁷⁰ In addition, the manufacturer was required to file a SDNA and

⁶⁷ See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1774-75 (1996) (describing extent of expansion of FDA authority under the 1962 Amendments). The expansion of regulatory power was so dramatic that “it would be difficult to exaggerate the significance of the shift in regulatory leverage that resulted from Congress’s adoption of a premarket approval scheme, and the FDA’s successful efforts to extend its coverage.” *Id.* at 1775. The United States has moved from a time when pharmaceutical manufacturers could market any products in any way so long as the claims were not false to a time wherein drugs can only be marketed after the FDA finds the drugs are safe and effective and approves the label and marketing. *Id.*

⁶⁸ See Helm, *supra* note 43, at 131-32 (discussing response to the new FDA regulatory structure). Pharmaceutical manufacturers argued that the increased expense and duration of the human clinical trials compromised productivity and marketplace competitiveness. *Id.* at 131. Many reform proponents believed, however, that the drug industry was operating under a business paradigm that, “if left unchecked, would certainly incur more drug-related injuries” and threaten the public health. *Id.* at 132. The FDA advocated the prophylactic purpose of the Amendments, arguing that it provided the medical community with sufficient knowledge about the safety and effectiveness of a drug before the drug was introduced to the marketplace. *Id.*

⁶⁹ See 21 C.F.R. § 314.70 (2011) (outlining changes and supplements to an approved application). When a new use is discovered and the drug sponsor wishes to have the new indication be approved by the FDA, they must file the supplemental application with the FDA, test the effectiveness of the new use before distributing the drug for the new use, and update all the labeling and marketing. *Id.* § 314.70(a). Even though the FDA created the SDNA to shorten approval time, pharmaceutical manufacturers still resisted the new requirements because it frequently took longer for the FDA to approve SDNAs than original NDAs. See Helm, *supra* note 43, at 134. The length of the approval time delayed the availability of new treatments to patients and hindered the manufacturers’ productivity. Additionally, filing SDNAs was expensive, and manufacturers passed these costs onto consumers by increasing prices. *Id.* at 134-35.

⁷⁰ 21 C.F.R. § 314.70(b) (2011). Changes requiring the filing of an SDNA include:

any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an

obtain FDA approval before changing the label of an approved drug or marketing a new aspect of a drug.⁷¹ Failure to file a SDNA and obtain FDA approval for any label change before introducing the drug to the market with the new label could result in withdrawal of the FDA's approval of the original NDA.⁷² The FDA now had the power to monitor all manufacturer labeling and promotion of new uses of pre-approved drugs to ensure that manufacturers complied with the SNDA requirements by seeking FDA-approval of the new uses and updated labeling.⁷³

adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

Id. § 314.70(b)(1). The definition of “change” includes but is not limited to:

changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application; (ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug; (iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation; (iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance.

Id. § 314.70(b)(2).

⁷¹ See 21 C.F.R. § 314.70(b)(2)(v) (requiring labeling changes to be submitted to the FDA for approval prior to distribution of the new labeling); 21 C.F.R. § 201.57 (2011) (detailing labeling requirements). The FDA must approve any and all changes in labeling, any change to a Medication guide. See 21 C.F.R. § 314.70(b)(2)(v)(A)-(C) (listing label changes that require a supplemental submission and approval). The new labeling must comply with FDA content and format specifications. See 21 C.F.R. § 201.57 (providing specific requirements on content and format of labeling).

⁷² Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355(e) (2010) (defining grounds for withdrawal of FDA approval). If the FDA does not approve the SDNA, they have the power to “order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.” 21 C.F.R. § 314.70(c)(7) (2011).

⁷³ See Helm, *supra* note 43, at 135 (describing effects of the SDNA process). Functionally, “the SNDA process served to further enhance the FDA’s regulatory control over drug labeling and the dissemination of information concerning appropriate drug use under that label to consumers and physicians.” *Id.* Manufactures used to be free to market their products and the FDA bore the burden of instituting legal proceedings if they questioned the safety or effectiveness of a drug and had to prove that the drug was dangerous or mislabeled. Merrill, *supra* note 67, at 1797 (summarizing the New Drug Approval system). In contrast, the FDA is now the gatekeeper of pharmaceutical marketing because the agency must now approve any promotional changes. *Id.*

Prior to the 1990s, the bulk of pharmaceutical marketing was directed exclusively at physicians.⁷⁴ Manufacturers employed pharmaceutical representatives, known as “detailers,” to influence physician prescribing habits, thereby increasing consumer sales of their drugs.⁷⁵ In the 1980s, pharmaceutical manufacturers argued that the FDA should allow DTC advertising because consumers needed access to the latest scientific information and knowledge.⁷⁶ Because the regulatory structure at the time did not expressly prohibit print advertisements and other broadcast mediums, the FDA announced that the same regulations governing the promotion of drugs to physicians would be sufficient to protect patients and consumers from false or misleading DTC advertisements.⁷⁷ The right to engage in DTC marketing was cemented in 1997 when the FDA changed its policy and made DTC advertising feasible for pharmaceutical

⁷⁴ Michael S. Wilkes et al., *Direct-To-Consumer Prescription Drug Advertising: Trends, Impact, and Implications*, 2 HEALTH AFFAIRS 110, 113 (2000), available at <http://content.healthaffairs.org/content/19/2/110.full.pdf>. The physician-patient relationship was very paternalistic during the bulk of the twentieth century, so direct promotions to the public were “inconceivable.” *Id.*

⁷⁵ Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 311 (1992) (explaining the importance of pharmaceutical detailing). Rather than “sell” prescription drugs, pharmaceutical detailers encourage physicians to use the products in their practices and to prescribe the products for their patients. *Id.* Detailers channel pertinent information to health care professionals by supplying physicians and pharmacists with articles and samples. *Id.* Even as late as the 1970s, the FDA understood that detailing was the “major source of continuing education” about pharmaceutical products for the practicing physician. *Id.*

⁷⁶ See Fox, *supra* note 66, at 1176-79 (presenting arguments in favor of and opposed to DTC marketing). Proponents claim that DTC marketing “improves communication between patients and healthcare providers” because the ads “encourage patients to engage their physician in dialogue” and to take a more active role in the decision making process. *Id.* at 1176. Additionally, mass media marketing may increase detection of “under-treated and under-diagnosed conditions such as arthritis, seasonal allergies, obesity, high cholesterol, osteoporosis, and depression” because advertisements prompt patients to request more information about conditions they did not know they had. *Id.* at 1176-77. Opponents of DTC marketing worried that the advertising would inflate health care costs and mislead physicians and the general public. *Id.* at 1177-78. People were additionally concerned that physicians and laypeople would misread the for-profit promotions as educational information. *Id.* at 1178.

⁷⁷ See *Direct-to-Consumer Advertising of Prescription Drugs; Withdrawal of Moratorium*, 50 Fed. Reg. 36,677 (Sept. 9, 1985). The FDA permitted consumer-oriented advertising via electronic and print media, so long as the advertising included “a brief summary of all necessary information related to side effects and contraindications in any advertisement that promotes a drug for a particular use.” *Id.* The FDA intended that the brief summary ensure a “fair balance” between promotion of the drug’s potential benefits and the risks of adverse side-effects. *Id.*

manufacturers.⁷⁸ Drug manufacturers jumped at the chance to promote their products, and DTC advertising swiftly became a hugely successful promotional tool.⁷⁹

III. Current FDA Regulation of Pharmaceutical Internet Promotions

When the FDA approves a pharmaceutical drug, the approval is only granted for the specific indications and therapeutic uses that were proven to be safe and effective in the clinical testing; any activity inconsistent with the FDA-approved labeling is considered “off-label.”⁸⁰ All off-label activity can be classified as off-label use, prescription, or marketing.⁸¹ Off-label use occurs when someone takes or utilizes a pharmaceutical drug or other medical therapy in a way that is inconsistent with the instructions on the FDA approved label.⁸² FDA regulation of off-label use is

⁷⁸ U.S. DEP’T OF HEALTH AND HUMAN SERVICES ET AL., GUIDANCE FOR INDUSTRY: CONSUMER-DIRECTED BROADCAST ADVERTISEMENTS (1999), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070065.pdf>.

So long as the advertisements were not false or misleading in any respect, presented a fair balance between information about effectiveness and about risk, and communicated the most important risk information and the indication or untended use in consumer-friendly language, the manufacturers would be in compliance with FDA labeling requirements. *Id.* at 2. Manufacturers also had to refer consumers either to a toll-free telephone number, their physician, a print advertisement, or a web site in the broadcast for further information on the FDA-approved labeling. *Id.* at 2-3.

⁷⁹ See Rosenthal et al., *supra* note 1, at 499 (researching industry wide trends in DTC promotion). Between 1996 and 2000, spending on DTC advertising tripled, reaching over \$2.5 billion. *Id.* at 499-500. Manufacturers spent seven times as much money on television advertisements by 2000 as they had spent in 1996. *Id.* at 500. Whereas promotion to physicians focuses on all brand-name drugs, DTC advertising concentrates on only a few products. *Id.* at 501. In 2000, only 20 prescription drugs accounted for about sixty percent of the total industry spending on DTC advertising. *Id.*

⁸⁰ See *Use of Approved Drugs for Unlabeled Indications*, FDA DRUG BULL., Apr. 1982, at 4, available at http://www.circare.org/fda/fdadrugbulletin_041982.pdf. Under the FDCA, once a drug’s marketing has been FDA-approved, it “may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug’s safety and effectiveness have been established and which FDA has approved.” *Id.* Therefore, any activity that is not part of the FDA-approved labeling is “off-label.” See also Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 186-88 (1999) (defining “off-label” and explaining the legislative and regulatory context).

⁸¹ See Salbu, *supra* note 80, at 188 (categorizing all off-label activity as either use, prescription or marketing); Fox, *supra* note 66, at 1164-65 (describing relationship between off-label use, prescription and marketing).

⁸² *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001) (defining off-label use as “use of a device for some other purpose than that for which it has been approved by the FDA”); *United States ex rel. Bennett v. Medtronic, Inc.*, 747 F. Supp. 2d 745, 751 (S.D. Tex. 2010) (explaining that use is off-label “[w]hen a medical device is approved for one purpose or

impracticable because it typically occurs in the privacy of one's own home, with or without the knowledge or consent of the prescribing physician, and with or without the knowledge or encouragement of the pharmaceutical manufacturer.⁸³ When physicians prescribe drugs or medical devices for therapeutic purposes other than those approved by the FDA, they engage in off-label prescription.⁸⁴ Providing prescriptions constitutes the practice of medicine, and the FDA has never purported to have the power to

indication and used outside this approved purpose"); *Washington Legal Foundation v. Kessler*, 880 F. Supp 26, 28 (D.D.C. 1995) (referring to "the use of a drug or device in a manner not approved by the FDA and not set forth in the product's labeling materials"). The most common off-label uses include: use of different doses than the approved dosage, use by people other than those for whom the drug was approved, use for conditions other than those listed on the FDA approved label, and use in unapproved combination with other drugs. See William L. Christopher, *Off-label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (explaining the various forms of off-label use). One of the most recognizable examples of off-label use is the practice of prescribing aspirin to prevent against heart attacks. See Peter Elwood et al., *Aspirin for Everyone Older Than 50?*, 330 BRIT. MED. J. 1440, 1441 (2005) available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC558385/pdf/bmj33001440.pdf>. Even though aspirin has received widespread confirmation in medical literature as an effective treatment for the prevention of heart attack, the FDA has never approved the drug for this indication. See *id.*; *Bayer Settles False-Advertising Claim: FTC v. Bayer Corp.*, 16 No. 10 ANDREWS PHARMACEUTICAL LITIG. REP. 7 (2001).

⁸³ Salbu, *supra* note 80, at 188-89 (discussing problems inherent in regulation of off-label use). Once a drug is physically in the hands of a patient, the way the drug is used is also in the hands of the patient. *Id.* at 189. Therefore deviant use typically occurs in privacy, without the knowledge of the prescriber. *Id.* Despite the inherent difficulty, it is possible to regulate off-label use; the use of illegal drugs is already prohibited. *Id.* at 189 n.44. Additionally, off-label use is broadly defined and includes everything from benign mistaken use of a drug to state of the art treatment. See Christopher, *supra* note 82, at 249 (describing off label drug use as "a descriptive gamut from 'clearly experimental use to standard therapy and even to state of the art treatment'"). The diversity of off-label use makes it difficult to evaluate and hard to regulate. *Id.* Furthermore, it is integral to the practice of medicine and frequently represents recommended practice, last-resort therapy, and first-line therapy. See James M. Beck & Elizabeth D. Azari, *FDA, Off-label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 79 (1998) (discussing value and propriety of off-label use); Randall S. Stafford, *Regulating Off-label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (explaining forms of off-label use in the health care industry).

⁸⁴ Alexander T. Tabarrok, *Assessing the FDA Via the Anomaly of Off-Label Drug Prescribing*, 5 INDEP. REV. 25 (2000), available at http://www.independent.org/pdf/tir/tir_05_1_tabarrok.pdf (describing off-label prescribing as "widespread"); Salbu, *supra* note 80, at 189 (explaining that "[o]ff-label prescription occurs when a doctor prescribes a drug in any manner that varies from the labeling specifications"); Fox, *supra* note 66, at 1164 (defining off-label prescription as "when a physician prescribes a drug in a manner inconsistent with its label"). The term includes prescribing drugs to different populations, for different therapeutic uses or treatments, for longer or shorter periods of time, or in combinations with other drugs that have not been FDA-approved. See Salbu, *supra* note 80, at 189.

regulate the prescribing decisions of physicians.⁸⁵ While the FDA does not regulate how a physician may prescribe a drug, the FDA does regulate off-label marketing and promotion by controlling the information that pharmaceutical manufacturers disseminate about their products.⁸⁶

Off-label marketing occurs when manufacturers promote or advertise their products for purposes, patients, dosages, or in combinations other than those that are approved by the FDA.⁸⁷ The FDA interprets “labeling” very broadly, and considers any information disseminated by or on behalf of the drug manufacturer to be part of the

⁸⁵ See Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 396 (2006) (stating that “nothing in this chapter [FDCA] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate practitioner-patient relationship”). It is the FDA’s policy to not limit the manner in which a physician may use an approved drug. See *Use of Approved Drugs for Unlabeled Indications*, *supra* note 80. The FDA acknowledges 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.” *Id.* Off-label prescribing is so prevalent that several studies estimate that forty to sixty percent of all prescriptions are written for unapproved uses, and one study found that most hospital patients are given at least one drug for use off-label. Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 978 (2007). New medical and technological discoveries take place much more rapidly than FDA-approval and frequently constituted the “best practice” standard of care. See Tabarrok, *supra* note 84, at 26 (explaining why physicians prescribe off-label). Patients also demand innovation when other FDA-approved uses fail, especially for illnesses such as AIDS, cancer and other life-threatening diseases. See *id.*; Fox, *supra* note 66, at 1165-66. In situations where the patient population is low, such as with rare diseases, “the financial costs of testing a new indication may outweigh the expected commercial benefits of FDA approval.” Fox, *supra* note 66, at 1166. Although physicians need the freedom to exercise their best medical judgment for their patients, manufactures nonetheless still financially profit from off-label prescribing. See Christopher, *supra* note 82, at 250 (arguing that pharmaceutical manufacturers are not pressured by the medical community to seek FDA-approval of the off-label uses that are already prescribed by physicians because the off-label uses are already generating revenues).

⁸⁶ See Salbu, *supra* note 80, at 190 (explaining that the scope of FDA authority extends to drug manufacturers but not to the physicians who dispense them); John N. Joseph et al., *Enforcement Related to Off-label Marketing and Use of Drugs and Devices: Where Have We Been and Where Are We Going?*, 2 J. HEALTH & LIFE SCI. L. 73, 77-79 (2009) (describing FDA regulatory power over off-label promotion).

⁸⁷ See Salbu, *supra* note 80, at 191 (defining off-label marketing as “when the manufacturers of the drugs promote or advertise their products for purposes, to users, in dosages or in combinations other than the FDA-approved ones”); Fox, *supra* note 66, at 1176 (explaining that most off-label marketing overstates the efficacy, broadens the indication, implies that the drug can be taken by a wider population than the approved population, or downplays the medical risks).

labeling.⁸⁸ As a result, the FDCA's prohibition of false or misleading labeling has become an effective prohibition on any advertisement, promotional message, or legitimate medical discussion that is inconsistent with the FDA-approved labeling.⁸⁹ Marketing traditionally includes direct sales pitches to physicians, advertisements, and product labeling.⁹⁰ The government will scrutinize the manufacturer's entire range of

⁸⁸ See Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 321(k), (m) (2006) (defining "label" and "labeling"); 21 U.S.C. § 352(a) (deeming a drug "misbranded" if the "label is false or misleading in any particular."). The FDA defines "label" expansively to include:

a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

Id. § 321(k). "Labeling" includes not only what is attached to the product but also anything that accompanies the drug or medical device. *Id.* § 321(m). When determining whether or not a drug has been misbranded because the labeling is misleading, the FDA shall review:

(among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

Id. § 321(n).

⁸⁹ See Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, 64074 (Dec. 3, 1997) (stating clearly that "the regulated industry cannot promote its products for unapproved uses, or . . . in ways not consistent with approved labeling"). The FDA has expanded its power to regulate labeling fraud by interpreting its own regulations as prohibiting communication between physicians or other health care providers and drug company representatives regarding any information that is not "consistent with" the approved product labeling. *Id.* This broad prohibition is not set forth in any single regulation, but stems from reading the combination of 21 U.S.C. § 355(a) (granting the FDA the power to regulate the product labeling prior to introducing it into interstate commerce) and the FDA-generated regulation found at 21 C.F.R. § 202.1(e)(4) (restricting the marketing and promotion of drugs in a manner inconsistent with their approved uses). See *id.*; 21 U.S.C. § 355(a) (2010); 21 C.F.R. § 202.1(e)(4) (2011).

⁹⁰ See Helm, *supra* note 43, at 148 (discussing history of pharmaceutical advertising). Until the late twentieth century, drug companies primarily promoted their products through advertisements in medical journals and sales promotions directed at physicians. *Id.* Since the FDA approved DTC promotion, advertisements have typically been channeled through mass media, primarily

conduct surrounding the distribution of a product, including (1) the content of traditional marketing mediums; (2) the extent of the manufacturer's involvement in scientific, academic, and continuing medical education conferences addressing off-label uses; (3) the funding of off-label research; (4) the distribution of medical journal articles addressing off-label studies; (5) and all other actions pertaining to the distribution of the drug, including statements of sales representatives.⁹¹ While some advertising is highly visible and relatively simple to regulate, such as advertising in professional journals, in mainstream print or broadcasting, and on product websites, other manufacturer practices are much more difficult to monitor. For instance, it is much more difficult to monitor whether manufacturers are providing grants to managed care organizations that encourage off-label prescriptions, hosting symposiums on unapproved drug uses, and encouraging discussions of off-label uses between physicians and pharmaceutical representatives.⁹² Even though the FDA has the power to regulate off-label marketing,

broadcast television. *Id.*

⁹¹ See 21 C.F.R. § 202.1(l) (2011) (defining scope of FDA-regulated advertising material). The FDA has comprehensive control over all advertising, including anything "in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems." *Id.* Specifically, the FDA must approve:

[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians 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.

Id. § 202.1(l)(2). Additionally, the FDA defines "promotional labeling" as anything related to the product. See *id.* (referring to section 201(m) of the Federal Food, Drug and Cosmetic Act, codified as amended at 21 U.S.C. § 321(m)).

⁹² See Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557-58 (2009) (describing mechanisms of off-label promotion and their relative detection). The activities that are the easiest to detect and observe are "[p]rofessional journal ads," "[m]agazine and newspaper ads," "[t]elevision and radio ads," and "[p]roduct website ads." *Id.* at 1557 fig.1. It is slightly more difficult to monitor brochures, visual and print sales ads, giveaways, and exhibits and presentations at conferences and continuing medical education events. *Id.* Activities that are the most difficult to detect include: "[r]esponses of company medical affairs offices to physicians' questions," "[p]resentations at company-sponsored events," "[o]ral statements of company representatives at exhibit booths," and "[o]ral statements of sales representatives during 'detailing' visits." *Id.* Oral statements are so difficult to detect and observe that the FDA relies heavily on whistleblowers, such as physicians who receive the communications and company

pharmaceutical manufacturers also have the First Amendment right to communicate truthful information about their products.⁹³ Under limited circumstances, the First Amendment protects the right of manufacturers to communicate truthful off-label information to physicians in the form of peer reviewed medical journal articles.⁹⁴

Under the FDCA and FDA drug labeling regulations, off-label marketing renders a drug “misbranded,” and pharmaceutical manufacturers face civil and criminal liability for introducing a drug into interstate commerce that is misbranded.⁹⁵ Misbranding is defined as making a false or misleading statement or failing to include

employees. *Id.* at 1558.

⁹³ See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 377 (2002). In 2002, the Supreme Court found speech-related provisions of the FDAMA unconstitutional, and held that drug advertising is entitled to First Amendment protection as commercial speech. *Id.* To address this right, the FDA expressly permits companies to distribute peer-reviewed scientific articles “in recognition of the public health value to healthcare professionals of receiving scientific and medical information.” *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*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (last updated Aug. 6, 2009). Additionally, the FDA “recognizes the value of having new indications and intended uses for products approved or cleared by FDA and encourages sponsors of medical products to seek such approvals or clearances.” *Id.*

⁹⁴ See *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*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (last updated Aug. 6 2009). See generally Mariestela Buhay, Comment, *Off-Label Drug Promotion is Lost in Translation: A Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell its Products*, 13 J. HEALTH CARE L. & POL'Y 459 (2010) (critiquing the FDA's new Guidance); Santosh V. Coutinho, Comment, *License to Promote, or Just What the Doctor Ordered?: The New FDA Guidance on Dissemination of Off-Label Reprints by Pharmaceutical Companies*, 28 TEMP. J. SCI. TECH. & ENVTL. L. 279, 284 (2009) (arguing that new Guidance “is a legitimate compromise that seeks to balance physician autonomy in the practice of medicine, the rights of the pharmaceutical industry in communicating off-label information, and mission of the FDA to protect public health”).

⁹⁵ See Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 331(a) (2006) (prohibiting “[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded”); 21 U.S.C. § 333 (imposing civil and criminal liability for FDCA violations). Specific intent to defraud or mislead is not an element of a misdemeanor conviction, essentially imposing strict liability for off-label marketing. See *id.* § 333(a)(1). Misdemeanor criminal violations carry a maximum sentence of one year in jail plus a \$1,000 fine. *Id.* Felony liability requires proof of specific intent to defraud or mislead, and carries a maximum sentence of five years in prison plus a \$10,000 fine. *Id.* § 333(a)(2).

“adequate directions for use” in the labeling.⁹⁶ The FDA has expanded the scope of misbranding to cover “intended uses,” which includes all objectively intended uses by the drug manufacturer referenced in labeling, advertising, and written or oral statements by company representatives.⁹⁷ If the FDA-approved labeling does not include each “intended use,” the drug is deemed misbranded because the manufacturer has failed to include adequate directions for every intended use in the FDA-approved label.⁹⁸ The FDA traditionally enforced the misbranding provisions with minor administrative actions, but the regulatory climate is changing due to a recent surge in criminal prosecutions generating record-breaking settlements.⁹⁹

⁹⁶ See *id.* § 352(a), (f) (describing different ways a drug can become “misbranded”). Generally, the drug or medical device will be deemed misbranded if the “labeling is false or misleading in any particular.” *Id.* § 352(a). Specifically, all labeling must bear “(1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application.” *Id.* § 352(f).

⁹⁷ See 21 C.F.R. § 201.128 (2011) (interpreting FDA policy on intended uses).

⁹⁸ See generally John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL’Y, L. & ETHICS 299, 309-10 (2010) (summarizing collective effect of FDA regulation under the FDCA); Alex T. Paradiso, Note, *Prosecutorial Regulation of Off-Label Promotion: Sidestepping the Courts and Congress to Levy a Tax on Suspect “Big Pharma” Marketing*, 60 SYRACUSE L. REV. 161, 170 (2009) (explaining sources and theories of civil and criminal liability under the FDCA).

⁹⁹ See Helm, *supra* note 43, at 177 (describing typical FDA enforcement); Paradiso, *supra* note 98, at 170. Typically, the FDA issued public Warning Letters, punitive and precautionary statements directed at the drug manufacturer. Helm, *supra* note 43, at 177. The Warning Letters created enough negative press that the government thought the written reprimands fit the crimes, and the FDA rarely instituted actual prosecutions. *Id.* The FDA began criminally prosecuting off-label marketing in 1999 when they brought suit against Genentech for the marketing of Protropin, a growth hormone. See Sentencing Memorandum, *United States v. Genentech, Inc.*, No. CR-99-0141 (N.D. Ca. 1999). Genentech admitted that it aggressively marketed Protropin for the treatment of burns, childhood obesity and kidney disorders, even though the FDA had only approved it for the long-term treatment of children with growth hormone deficiency. *Id.* Genentech agreed to a landmark settlement of over \$50 million (\$30 million in criminal fines and \$20 million in civil settlement). *Id.* Since then, other settlements have reached astronomical heights. See Press Release, U.S. Dep’t of Justice, *Elan Pharmaceuticals Pleads Guilty, Sentenced for Off-Label Marketing of Zonegran* (Feb. 28, 2011), <http://www.justice.gov/usao/ma/news/2011/February/ElanSentencingPR.html> (settling for \$203.5 million); Press Release, U.S. Dep’t. of Justice, *Forest Pharmaceuticals Sentenced to Pay \$164 million for Criminal Violations* (Mar. 2, 2011), <http://www.justice.gov/opa/pr/2011/March/11-civ-270.html> (totaling \$313 million for criminal and civil liability). Between 2009 and 2010 the FDA and DOJ recovered a total of \$9 billion. See Press Release, U.S. Dep’t of Justice, *Pharmaceutical Manufacturers to Pay \$421.2 Million to Settle False Claims Act Cases* (Dec. 7, 2010), <http://www.justice.gov/opa/pr/2010/December/10-civ-1398.html>. In December 2010 alone, settlements totaled more than \$701 million. See Press Release, U.S. Dep’t. of Justice,

In addition to liability under the FDCA, pharmaceutical manufacturers face liability under the Federal False Claims Act (“FCA”).¹⁰⁰ The FCA makes it a federal crime to file, or cause to be filed, a false or fraudulent claim to be paid for by the government.¹⁰¹ The theory for prosecution under the FCA is that when manufacturers engage in off-label marketing in violation of the FDCA, they do so with the specific intent to cause physicians to prescribe off-label.¹⁰² This, in turn, causes fraudulent claims for reimbursement to be filed with Medicare and Medicaid that would not normally be paid.¹⁰³ Under this construction, even truthful and non-misleading statements made by manufacturers about the effectiveness of their drug for off-label uses will be deemed fraudulent under the FCA if they are submitted to the federal government for reimbursement.¹⁰⁴ The FCA provides treble damages and fines of up to

Pharmaceutical Manufacturer to Pay \$280 Million to Settle False Claims Act Case, U.S. DEP’T OF JUST. (Dec. 20, 2010), <http://www.justice.gov/opa/pr/2010/December/10-civ-1464.html>.

¹⁰⁰ See Federal False Claims Act, 31 U.S.C. § 3729 (2006); see also Joseph et al., *supra* note 86, at 83 (arguing that “DOJ agents and prosecutors are fueled by their perception that enormous financial recoveries, including treble damages, can be—and have been—achieved through the vehicle of the False Claims Act”); Aaron S. Kesselheim et al., *False Claims Act Prosecution Did Not Deter Off-Label Drug Use in the Case of Neurontin*, 30 HEALTH AFF. 2318, 2325 (2011) (noting the limits of the FCA on deterring false claims); Paradiso, *supra* note 98, at 174 (citing the FCA as the other major source of civil liability in addition to the FDCA).

¹⁰¹ See 31 U.S.C. § 3729(a) (imposing liability for knowingly presenting, or causing to be presented, a false or fraudulent claim to the federal government for payment or approval). Congress enacted the FCA after the Civil War in an attempt to combat fraudulent claims that were being submitted to the federal government. See Joan H. Krause, “Promises to Keep”: *Health Care Providers and the Civil False Claims Act*, 23 CARDOZO L. REV. 1363, 1369 (2002). In the health care context, the FCA imposes liability on physicians, hospitals, and managed care organizations for preparing and/or submitting false claims for government reimbursement. *Id.* at 1370.

¹⁰² See *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 39, 44-45 (D. Mass. 2001) (describing FCA liability for off-label marketing).

¹⁰³ See *id.* at 45 (imposing FCA liability for off-label marketing).

¹⁰⁴ *United States ex rel. Franklin v. Parke-Davis*, No. 96-11651PBS, 2003 WL 22048255, at **4-5 (D. Mass. Aug. 22, 2003) (holding that § 3729(a)(1) does not require the “cause” to be fraudulent or otherwise independently unlawful). But see Ralph F. Hall & Robert J. Berlin, *When You Have a Hammer Everything Looks Like a Nail: Misapplication of the False Claims Act to Off-Label Promotion*, 61 FOOD & DRUG L.J. 653, 658-59 (analyzing FCA liability for truthful off-label statements). Even though a statement may be truthful, it may still be deemed fraudulent simply because it promotes off-label use, or outside the FDA-approved labeling. See *id.* at 658. Even though physicians are free to prescribe off-label, the manufacturers face severe federal civil liability if the federal government has reimbursed claims associated with off-label uses. *Id.* Although no appellate court has ever held a manufacturer liable for truthful off-label claims, manufacturers settle because the financial risk is not worth the cost of challenging the regulatory structure. See *id.* at 659.

\$10,000 per claim.¹⁰⁵ Either the government or a private individual whistleblower, known as a *qui tam* reator, may bring a FCA action against a manufacturer.¹⁰⁶ If the whistleblower brings suit and exposes the off-label activity, the government then has the option of joining and taking control of the suit, and the *qui tam* reator will be awarded fifteen to twenty-five percent of any recovery.¹⁰⁷ If the government does not join the suit, then the *qui tam* reator will walk away with twenty-five percent of the damages, a powerful incentive for exposing fraudulent manufacturer activity that is otherwise elusive and hard to detect.¹⁰⁸

In order to comply with FDA regulations, all labeling content must be submitted to the FDA for approval before it is introduced into interstate commerce.¹⁰⁹ All advertising, whether directed at physicians and health care professionals or the general public, must include the name of the drug, at least one FDA-approved use, and the most significant risks of the drug.¹¹⁰ The advertisement must present “a true

¹⁰⁵ 31 U.S.C. § 3729(a)(1) (prescribing a maximum penalty of \$10,000 plus three times the amount of damages awarded). Because health care providers submit several small claims every year rather than a few large claims, total damages can reach extremely high amounts. See Krause, *supra* note 101, at 1370 & n.23.

¹⁰⁶ 31 U.S.C. § 3730(a)-(b) (2010). Both the Attorney General and private persons have standing to bring a FCA suit. *Id.* A *qui tam* reator may be awarded a percentage of any award made by the court for damages and penalties, plus reasonable expenses, fees and costs, with the government retaining the balance. See *id.* § 3730 (d)(1)-(2).

¹⁰⁷ *Id.* § 3730(c). The government has the discretion to decide if they want to proceed with the suit once the reator exposes the allegedly fraudulent conduct. See *id.* “[D]epending upon the extent to which the person substantially contributed to the prosecution of the action,” they will receive between fifteen and twenty-five percent of the proceeds. *Id.* § 3730(d)(1).

¹⁰⁸ *Id.* § 3730(d)(2) (awarding the person who brings a successful FCA action “an amount which the court decides is reasonable” between twenty-five and thirty percent). Considering that settlements have reached hundreds of millions of dollars, a twenty-five percent recovery could potentially mean millions for the whistleblower. See *supra* note 99 and accompanying text.

¹⁰⁹ See 21 C.F.R. § 314.70(b)(2)(v) (2010) (requiring labeling changes to be submitted to the FDA for approval prior to distribution of the new labeling); *supra* note 71 and accompanying text; see also U.S. FOOD & DRUG ADMIN., *Background on Drug Advertising*, <http://fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm071964.htm#ddmac> (last updated April 5, 2010). The FDA has established the Division of Drug Marketing, Advertising and Communications (DDMAC) to “oversee prescription drug activities.” *Id.* Specifically, the DDMAC searches for and takes action against advertisements that violate the law, educates the pharmaceutical industry and others about the specifics of the law, and encourages better communication of promotional material directed at physicians and the general public. *Id.*

¹¹⁰ See Food, Drug, and Cosmetics Act 21 U.S.C. § 352(n) (2010); 21 C.F.R. § 202.1 (2010). The FDCA requires all prescription drug advertisements and all other printed material to include

a true statement of (1) the established name as defined in paragraph (e) of this

statement of information in brief summary relating to side effects, contraindications, and effectiveness,” commonly referred to simply as the “brief summary.”¹¹¹ The promotions may not be false or misleading in any respect, and all efficacy and risk information must be presented in a “fair balance.”¹¹² A claim will be considered false or misleading if the manufacturers promote uses that have not been approved by the FDA, omit material information relating to the risks of the promoted use, or make statements comparing their drug to others without “substantial” evidence from clinical trials supporting the claim.¹¹³ To be a “true statement,” the advertisements must present a fair balance

section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under paragraph (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness.

21 U.S.C. § 352(n) (2010). The FDCA does not distinguish between promotions directed at health care professionals and at consumers. *Id.* A recent FDA Draft Guidance addressing the presentation of risk information in advertising and promotion applies to promotions directed at both physicians and consumers. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION, at 1 (May 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>.

¹¹¹ 21 U.S.C. § 352(n)(3) (2010); 21 C.F.R. § 202.1(e)(1) (2010). Specifically, all advertisements “shall present a true statement of information in brief summary relating to side effects, contraindications and effectiveness.” 21 C.F.R. § 202.1(e)(1). Side effects and contraindications include “side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.” *Id.* The FDA explains “brief summary” as “the technical name for the detailed information that appears in advertisements for prescription drugs.” U.S. Food & Drug Admin., *Drug Advertising: A Glossary of Terms*, FDA.GOV (Jun. 24, 2009), http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm#brief_summary. Commonly, the brief statement includes: who should not take the drug, when the drug should not be taken, possible serious side effects of the drug and what can be done to lower the possibility of having the side effects, and frequently-occurring, non-serious side effects. *Id.*

¹¹² 21 C.F.R. § 202.1(e)(5) (2010). The brief summary will not be found to be a “true statement of information” relating to side effects, contraindications, and effectiveness if “it is false or misleading with respect to side effects, contraindications, or effectiveness.” *Id.* § 202.1(e)(5)(i). Additionally the brief statement must “present a fair balance between information relating to side effects and contraindications.” *Id.* § 202.1(e)(5)(ii).

¹¹³ *Id.* § 202.1(e)(6)(i). Advertisements cannot represent or suggest “that a drug is better, more effective, useful in a broader range of conditions or patients, . . . safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience.” *Id.* § 202.1(e)(6). In addition to evaluating the advertisements language, the FDA will also consider the form and “theme of the advertisement.” *Id.* § 202.1(e)(3)(i).

between the positive benefits and negative side effects of the drug.¹¹⁴ Furthermore, the use and risk disclosure must be in consumer-friendly language.¹¹⁵

The FDA distinguishes between print and broadcast advertisements.¹¹⁶ Print advertisements must include the brief summary, which usually includes each of the major FDA-approved uses and risks.¹¹⁷ Under Food and Drug Administration Amendments Act of 2007, all print advertisements must also incorporate the phrase: "You are encouraged to report negative side effects of the prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088."¹¹⁸ Broadcast promotions distributed through mass media, such as television, radio, or telephone communication systems, must disclose the product's major risks in either the audio (spoken aloud as part of the voice over) or visual parts of the advertisement.¹¹⁹ This is commonly known as the "major statement" requirement.¹²⁰ Broadcast advertisements must include the brief statement, or make an "adequate provision . . . for dissemination of the approved or package labeling in connection with the broadcast presentation" in order to satisfy the information disclosure requirements.¹²¹ The FDA recommends including a toll-free telephone number, an address where consumers can access the full labeling, a web page address, and the disclosure that the prescribing physician can provide the consumer with more information to satisfy the "adequate presentation"

¹¹⁴ *Id.* § 202.1(e)(5)(ii).

¹¹⁵ See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION, at 7 (May 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>. Language must be appropriate for the target audience to be accurate and non-misleading. *Id.* Therefore, promotional materials directed at physicians and health care professionals may use medical language, but promotional materials directed at consumers and the general public must use "language understandable to customers." *Id.* For example, the FDA recommends using "fainting" instead of "syncope" in advertising to the general public. *Id.*

¹¹⁶ See 21 C.F.R. § 202.1(e)(1) (regulating print and broadcast advertisements differently).

¹¹⁷ See *supra* note 111 and accompanying text.

¹¹⁸ Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. § 352(n)(3) (2010). All "published direct-to-consumer advertisements" must have the statement requesting users to report negative side-effects "printed in conspicuous text." *Id.*

¹¹⁹ 21 C.F.R. § 202.1(e)(1).

¹²⁰ See U.S. Food & Drug Admin., *Drug Advertising: A Glossary of Terms*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm> (last visited Feb. 1, 2012). In its definition, the FDA states that a "major statement" is only applicable to television and radio advertisements. *Id.* In these forums, presentation of the drug's most important risks "must be spoken." *Id.*

¹²¹ 21 C.F.R. § 202.1(e)(1).

requirement.¹²²

Most pharmaceutical ads are Product Claim advertisements, but the FDA also has created two additional classes: Reminder and Help-Seeking advertisements.¹²³ Whereas Product Claim advertisements name the drugs and describe the indications and any side-effects, Reminder advertisements “call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product.”¹²⁴ Reminder advertisements are exempt from the brief summary requirement because they do not specify the uses of the drug, and therefore do not need to include

¹²² See U.S. FOOD & DRUG ADMIN. DIVISION OF DRUG MARKETING ADVERTISING AND COMMUNICATION (DDMAC), *GUIDANCE FOR INDUSTRY CONSUMER-DIRECTED BROADCAST ADVERTISEMENTS*, 2-4 (Aug. 1999), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070065.pdf>. When the customer calls the toll-free telephone number, they “should be given the choice of: [h]aving the labeling mailed to them in a timely manner (e.g., within 2 business days for receipt generally within 4-6 days); or [h]aving the labeling read to them over the phone (e.g., by offering consumers a selection of prerecorded labeling topics).” *Id.* at 2. The FDA requires a physical address where consumers can access the labeling in order to address the concern that not all customers will have access to the Internet to get the full information. *Id.* at 3.

¹²³ See 21 C.F.R. § 202.1(e)(2)(i); U.S. Food & Drug Admin., *Prescription Drug Advertising*, FDA.GOV (June 24, 2009), <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/default.htm> (providing examples of Product Claim, Reminder, and Help-seeking advertisements).

¹²⁴ 21 C.F.R. § 202.1(e)(2)(i).

[R]eminder advertisements shall contain only the proprietary name of the drug product, if any; the established name of the drug product, if any; the established name of each active ingredient in the drug product; and, optionally, information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the advertised drug product.

Id. As an example, a manufacturer may use reminder advertising to provide price information to consumers without meeting all of the other labeling requirements if certain other conditions are met. *Id.* § 200.200(a). Typical reminder ads may simply state “[a]sk your doctor about” and the name of the drug being promoted. U.S. Food & Drug Admin., *Reminder Ad (Correct)*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm083573.htm> (last visited Feb. 1, 2012) (displaying a sample reminder advertisement in compliance with FDA regulations). In contrast, the FDA interprets graphics and phrases that suggest what the drug does to be “use” information; if the advertisement includes these types of suggestive communications than the advertisement must include associated risk information. U.S. Food & Drug Admin., *Incorrect Reminder Ad*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm082287.htm> (last visited Feb.1, 2012) (displaying a sample non-compliant reminder advertisement).

the relevant associated risks and contraindications.¹²⁵ Help-Seeking advertisements describe a medical condition or disease without recommending or promoting specific drugs.¹²⁶ Help-Seeking advertisements are exempt from FDA regulation; they do not fall within the definition of “prescription drug advertisements” because no specific drugs are ever mentioned.¹²⁷

Although the regulations and guidance documents distinguish between different forms of advertising based on content, the FDA has never specifically delineated between different advertising mediums.¹²⁸ Therefore, all Internet marketing is regulated under the existing regulatory scheme, and companies must adhere to the general requirements for all promotional material.¹²⁹ The FDA first specifically addressed the Internet promotion of FDA-regulated drugs and medical devices fifteen years ago in a public meeting.¹³⁰ The public discussion included panels addressing the presentation of

¹²⁵ See 21 C.F.R. § 202.1(e)(2). This C.F.R. exempts reminder advertisements from labeling requirements. *Id.* There does not need to be a fair balance between the efficacy and risk statements because the ad does not have efficacy statements by definition. *Id.*; see also FDA, *Incorrect Reminder Ad*, *supra* note 124 (“reminder ad does not contain risk information about the drug because the ad does not discuss the condition being treated or how well it works”).

¹²⁶ U.S. Food & Drug Admin., *Correct Help-Seeking Ad*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm082288.htm> (last visited Feb. 1, 2012). A typical help-seeking ad may describe symptoms and encourage patients to talk to their doctor for more information. *Id.* They may also include the name of the pharmaceutical manufacturer and provide a phone number for patients seeking more information. *Id.*

¹²⁷ See 21 C.F.R. § 202.1(b)(1) (requiring name of drug to be included in promotional advertising); FDA, *Correct Help-Seeking Ad*, *supra* note 126. “[The] FDA does not regulate lawful help-seeking ads.” *Id.*

¹²⁸ Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. 48083, 48085 (Sept. 21, 2009). No FDA formal rule has ever addressed the Internet specifically, but the FDA has long considered it to be “fairly clear that some [Internet] promotional efforts are substantially similar in presentation and content to promotional materials in other media or publications.” *Id.* at 48085. See generally Betsy McCubrey & Christine Forgues, 404: *Server Error – Cannot Find Regulations (Yet): Pharmaceutical Companies Must Stay Apprised of FDA’s Social Media Enforcement and Guidance Efforts*, 12 J. HEALTH CARE COMPLIANCE no. 2 at 55, 56 (2010) (noting “[a]pplicable FDA statutes and regulations do not, *per se*, prohibit certain types of media”).

¹²⁹ See Abrams, *supra* note 8, at 9. When asked how the FDA will apply DTC advertising regulations to Internet and social media marketing, the DDMAC replied, “[t]hese [FDA laws, regulations, and] rules apply regardless of the medium used for dissemination.” *Id.*

¹³⁰ U.S. Food & Drug Admin., *Transcript of Internet Public Meeting: Advertising and Promotion of Medical Products*, FDA.GOV (June 24, 2010), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm175775.htm>. The meeting took place on October 16, 1996 and October 17, 1996. *Id.* Given “recent dramatic increases in the number of

unapproved uses of approved products, communications in Internet chat rooms, general regulatory issues, hyperlinks, and international issues.¹³¹ Despite the overwhelming need for regulatory clarification, the FDA did not promulgate either regulations or guidance documents explaining the FDA's policy on Internet marketing following the 1996 meeting.¹³² Thirteen years later, in November 2009, the FDA held another public hearing to discuss Internet promotion, specifically calling for information on the use of social media for marketing pharmaceuticals and medical devices, but has yet to issue regulations or guidance documents that encompass a broad scope of Internet-specific advertising.¹³³ The industry expected the FDA to publish a draft guidance document

users of the Internet, including the Web, [and the fact that] companies, including manufacturers and distributors of products regulated by FDA, [were] looking at the Internet as a medium for disseminating information about their products[.]” the FDA sought to determine “how the statutory provisions, regulations, and policies concerning advertising and labeling should be applied to product-related information on the Internet and whether any additional regulations, policies, or guidances [were] needed.” Promotion of FDA-Regulated Medical Products on the Internet; Notice of Public Meeting, 61 Fed. Reg. 48,707 (Sept. 16, 1996). Before calling the public meeting, the FDA consulted with companies, third-party providers, and others to expand the FDA's understanding of the technical aspects of Internet marketing. *Id.*

¹³¹ U.S. Food & Drug Admin., *Transcript of Internet Public Meeting: Advertising and Promotion of Medical Products*, FDA.GOV (June 24, 2010), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm175775.htm>. Due to industry confusion, the FDA specifically sought input regarding the fair balance requirement, whether or not hyperlinks should be allowed at all, and the effect of third-party dissemination of information about off-label uses before the meeting. Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools, 74 Fed. Reg. at 48,707-09.

¹³² See Emilé L. Loza, Note, *FDA Regulation of Internet Pharmaceutical Communications: Strategies for Improvement*, 55 FOOD & DRUG L.J. 269, 273 (2000). Even though the industry was “screaming for guidance” in 1996, the “FDA has not prioritized the need for regulatory clarification in the Internet context.” *Id.* Despite critiques of the FDA, the FDA failed to offer comprehensive guidance, leading one author to argue that, given the Internet's expanding role, particularly as a source of healthcare information, “[i]f the agency persists in its silence, problems of Internet drug promotion likely will expand in the years to come.” Leah Brannon, *Regulating Drug Promotion on the Internet*, 54 FOOD & DRUG L.J. 599, 602 (1999).

¹³³ See Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,083-85 (2009); FDA, *Public Hearing on Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools*, FDA.GOV (Dec. 27, 2011), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm184250.htm>. The public hearing was held on November 12 and 13, 2009. U.S. Food & Drug Admin., *Public Hearing on Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools*, FDA.GOV (Dec. 27, 2011), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm184250.htm>. The agency's objective was to receive broad public input and to hear various points of view and opinions on Internet issues from a discussion among interested persons including “consumers, patients, caregivers, health care professionals, patient groups, Internet

addressing a wider scope of Internet marketing in 2010 following the 2009 public hearing.¹³⁴ In December 2011, the FDA published a draft guidance document addressing the limited topic of unsolicited requests for off-label information about prescription drugs.¹³⁵ The guidance document looked at the use of emerging electronic media, but it only considered responses to unsolicited requests for information, and not the use of social media or other technology generally.¹³⁶

Even though the FDA regulates Internet advertising under the current regulatory scheme, several features of Internet advertising differentiate it from traditional marketing mediums.¹³⁷ Despite commonalities with print advertising, such as

vendors, advertising agencies, and the regulated industry.” *Id.* The FDA noted the entry of new internet tools and technology since its 1996 public meeting, including blogs, microblogs, podcasts, social networks and online communities, video sharing, widgets, and wikis. *Id.* at 48,085. In 2009, the FDA published a draft guidance on risk information in promotions but only mentioned the Internet in a footnote and used a hypothetical web site in an example. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION 3 n. 9, 14 (2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>. The FDA made it clear that they intend every mention of promotional materials to encompass all promotional materials, “regardless of format,” including the internet. *Id.* at n.9. However, this guidance document only discussed “Internet web sites” and did not address any Internet-specific gray areas, like hyperlinking. *Id.*; see also *supra* notes 128-129 and accompanying text; *infra* notes 137-152.

¹³⁴ See McCubrey & Forgues, *supra* note 128, at 55-56 (explaining the 2009 meeting “led many to believe the FDA will be releasing guidance on the issue”). The FDA may issue several guidance documents relating to social media rather than one comprehensive guidance document to give the FDA more regulatory flexibility. See *DDMAC: Social Media Guidance Likely To Be Split into Multiple Documents*, THOMPSON (June 15, 2010), <http://www.thompson.com/public/newsbrief.jsp?cat=FOODDRUG&id=2906>. See also Hollie A. Smith et al., Commentary, *Are Your Meta Tags Showing? Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools*, 27 WESTLAW J. PHARMACEUTICAL 10 (2011) (discussing possible FDA future action).

¹³⁵ U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES (2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>. The guidance is not final and has only been distributed for comment purposes. *Id.*

¹³⁶ See *id.*

¹³⁷ See Loza, *supra* note 132, at 284 (2000) (reviewing “difficulties that emerge when shoehorning Internet drug sites into advertising regulations designed for traditional media”). The definitions developed for traditional print advertising, the evolving use of potentially misleading graphics, the fair balance requirement, and the adequate provision requirement are all areas that have vexed the industry and made it difficult to anticipate what the FDA will consider to be in compliance with existing regulations. *Id.* at 284-86.; see also Brannon, *supra* note 132, at 615-18 (analyzing “unique enforcement challenges” stemming from Internet activity); McCubrey & Forgues, *supra* note 128,

the use of text, the Internet also has several features of broadcast advertising, such as video streaming.¹³⁸ Internet tools and technology now enable pharmaceutical manufacturers to advertise and promote their products through Internet platforms such as blogs, microblogs (like Twitter), podcasts, social network sites (“social networks”) and online communities, video sharing, widgets, and wikis.¹³⁹ Several of these technologies

at 55 (describing impact of Internet on consumer expectations).

¹³⁸ See Jeffrey M. Senger, *Emerging Issues in FDA Regulation: Warning Letters, Internet Promotion, and Tobacco*, 13 J. HEALTH CARE L. & POL’Y 211, 218 (2010) (“[w]hile some Internet promotional efforts are substantially similar in presentation and content to promotional materials in traditional media, others are not”); James M. Wood & Howard L. Dorfman, *“Dot.Com Medicine” — Labeling in an Internet Age*, 56 FOOD & DRUG L.J. 143, 147 (2001) (describing the Internet as “a hybrid of print and electronic communication”). For example, blogs can consist of text, images and videos, podcasts can be either audio or visual, and video sharing allows users to upload their own video content. Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,085 (outlining different types of technology and the associated content with each).

¹³⁹ Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,085. The FDA defines “blogs” like Blogger, WordPress, and TypePad as

Web sites with regular updates (in reverse chronological order—newest update at the top) that typically combine text, images (graphics or video), and links to other Web pages. Blogs are usually informal and take on the tone of a diary or journal entry. Some blogs are very personal, while others provide mainstream news updates. Most blogs encourage dialogue by allowing their readers to leave comments.

Id. Microblogs, like Twitter, are “comprised of extremely short written blog posts, similar to text messages, and provide real-time updates.” *Id.* A Podcast is a type of shared audio or video file

that users can listen to or watch on computers or on a variety of portable media devices (like an iPod, Zune, and certain cell phones). Podcasts are usually short and often free, and users can arrange via subscription to receive new podcasts automatically via their computers or other media devices.

Id. Websites such as Facebook, MySpace, and LinkedIn are social networks and online communities that

give users opportunities to connect with or provide resources to clients, colleagues, family, and friends who share common interests. In many social networks, users create profiles and then invite people to join as “friends.” There are many different types of social networks and online communities, many of which are free, and they range from general to those tailored for a specific demographic or interest area.

Id. Video sharing sites, like YouTube, “allow[] individuals to upload video clips to an Internet Web site. The video host will then store the video on its server and show the individual different

limit the number of characters that can be used, and manufacturers have had to creatively face these challenges when marketing with social media like Twitter.¹⁴⁰ An additional concern for the industry is the ease with which the Internet enables third-party creation and dissemination of on-label and off-label information, something that was more expensive and time consuming when the regulations were developed.¹⁴¹

types of code to allow others to view or comment on the video.” *Id.* A “widget” is described as a graphic control on a Web page that allows the user to interact with it in some way. Widgets can also be easily posted on multiple Web sites, have the added benefit of hosting “live” content, and often take the form of on-screen tools (clocks, event countdowns, auction tickers, stock market tickers, flight arrival information, daily weather, etc.).

Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,085. With roots in the Hawaiian word for “fast,”

[w]iki technology creates a Web page that anyone with access can modify—quickly and easily. A wiki can be either open or closed, depending on the preferences of the community using it. An open wiki allows anybody to make changes and view content. A closed wiki allows only community members to make changes and view its content. Some wikis allow anyone to view content but only members to edit the content.

Id. To better understand “the nature of, and the technical aspects to, promotion of FDA-regulated medical products using [the above-described] tools,” the FDA has consulted with “companies, third-party providers, trade associations, and other groups.” *Id.*

¹⁴⁰ See Senger, *supra* note 138, at 218-19 (questioning how companies “can meet their regulatory obligations given the real-time nature and space limitations of certain Internet communication tools”); Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,086 (insinuating potential challenges exist in fulfilling regulatory requirements when using tools that limit space). Twitter messages, or “Tweets,” must be 140 characters or less. *About Tweets (Twitter Updates)*, TWITTER, <http://support.twitter.com/groups/31-twitter-basics/topics/109-tweets-messages/articles/127856-about-tweets-twitter-updates> (last visited Feb. 4, 2012). Google’s “Ad Sitelinks” and “AdWords” (short advertisements on search result pages with links to company web pages appearing above or to the side) limit advertisers in most languages to twenty-five characters in the headline and thirty-five characters on each of two description lines. See generally *Ad Format – Advertising Policies Help*, GOOGLE, <http://support.google.com/adwordspolicy/bin/static.py?hl=en&topic=1310862&guide=1308145&page=guide.cs> (last visited Feb. 4, 2012) (providing Ad Sitelink requirements); *Character Limit – Advertising Policies Help*, GOOGLE, <http://support.google.com/adwordspolicy/bin/static.py?hl=en&topic=1310862&guide=1308145&page=guide.cs&answer=175910> (last visited Feb. 4, 2012) (providing AdWords requirements).

¹⁴¹ Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Fed. Reg. at 48,086-88 (raising particular issues affecting what online communications can be attributed to manufacturers, packers, or

One of the more controversial issues between the industry and the FDA has been the applicability of the fair balance requirement use of hyperlinks.¹⁴² Current regulations specify that the brand name must appear linked to the generic name of a drug at least once per “page.”¹⁴³ The concept of an “Internet page,” however, does not fit smoothly into the traditional definition of a printed “page.” An Internet page is normally “understood as a single, continuous document comprised of text, graphics and hyperlinks; it is not organized into discreet viewing units like a magazine.”¹⁴⁴ Therefore,

distributors). The FDA was also concerned with what parameters should be applied when companies exert substantive influence on third-party communications and how companies should disclose their involvement or influence over discussions or material. *Id.* Recognizing the “potential for company communications to be altered by third parties,” the FDA wanted to know “the experience to date with respect to the unauthorized dissemination of modified product information (originally created by a company) by noncompany users of the Internet.” *Id.* at 48,086. For the 2009 public hearing, the FDA specifically sought input regarding when third-party discussions should “be treated as being performed by, or on behalf of, the companies that market the product, as opposed to being performed independent of the influence of the companies marketing the products.” *Id.*; see also McCubrey & Forgues, *supra* note 128, at 55. “[T]hird parties with no ties to the pharmaceutical company are developing their own content on the company’s products.” *Id.*; Brannon, *supra* note 132, at 607 (identifying “the fact that on the Internet manufacturers are not the only suppliers of information” as a primary concern when developing regulations).

¹⁴² See Peter S. Reichertz, *Legal Issues Concerning the Promotion of Pharmaceutical Products on the Internet to Consumers*, 51 *FOOD & DRUG L.J.* 355, 360 (1996) (outlining legal issues with FDA Internet regulation). The FDA and the industry have been debating the use of hyperlinks since the early 1990s. *Id.* Initially, the FDA was primarily concerned about links to Internet sites discussing off-label uses and activity. *Id.* The FDA stated at the time that the manufacturer would be in violation of regulations if they posted a link to a site discussing an off-label use. *Id.* By 2000, hyperlinks still presented compliance problems. See Loza, *supra* note 132, at 285-286 (discussing difficulties of applying current FDA fair balance requirement to Internet advertising). Rather than linking to third-party sites, the FDA was becoming more concerned with the brief summary requirement and the way companies presented their own risk information. *Id.* at 285. Companies made broad efficacy statements and then provided a hyperlink to the corresponding risk information. *Id.* Rather than presenting the information in a meaningful way, many manufacturers were tempted to bury risk information in hyperlinks. *Id.* at 286.

¹⁴³ See 21 C.F.R. § 202.1(b)(1) (2010). Alternatively, the regulations require the pairing of generic and brand names once per column of advertising text. *Id.*; see also *id.* § 202.1(e)(7)(ix)(xi) (discussing the emphasis and display of negative product information on facing pages). If the brand name is featured, the generic name must “accompany” it. *Id.* § 202.1(b)(1). If the brand name is used in the running text (not featured), the generic name must appear at least once in the same size type on any page. *Id.* The regulations further specify that if the drug is mentioned in any column of advertising text, the generic name must also be printed in the same text column. *Id.* Labeling regulations have a similar requirement. See 21 C.F.R. § 201.10(g)(1) (2010).

¹⁴⁴ Loza, *supra* note 132, at 284 (defining “Internet page”). The difference between an Internet

the issue becomes whether or not a hyperlink is part of the same “page” or is a separate “page.”¹⁴⁵ This same definitional problem gives rise to potential problems with the “fair balance” requirement, because it is not clear whether all of the uses and risks have to appear on the same “page” or whether a hyperlink to the risk information will satisfy the disclosure requirements.¹⁴⁶

Many pharmaceutical manufacturers postulated that providing a hyperlink to the risk information in close proximity to the efficacy statements would constitute a fair balance and true statement because the risk information was only “one-click” away; many in the industry began referring to this as the “one-click” rule.¹⁴⁷ Despite a lack of clear guidance about the use of hyperlinks, the FDA continued with enforcement actions.¹⁴⁸ In 2009, the FDA sent fourteen warning letters to pharmaceutical

page and an Internet website is not always clear to laypeople. *Webpage*, TECHTERMS.COM, <http://www.techterms.com/definition/webpage> (last visited Jan. 31, 2012). An Internet page is a singular HTML document whereas a website is a collection of pages. *Id.*

¹⁴⁵ See Loza, *supra* note 132, at 285 (identifying definitional problems with application of fair balance requirement). Hyperlinks muddy the distinction between a site and a page. *Id.* Drug advertisements must include information for all claimed purposes, and untrue or misleading information in one part of the advertisement cannot be reconciled by including the brief summary in another part. 21 C.F.R. § 202.1(e)(3)(i)-(iii) (2010). This also applies to an advertisement’s theme. *Id.* However, the FDA has never defined “one part of the advertisement.” See *id.*

¹⁴⁶ See Loza, *supra* note 132, at 285 (identifying problems with application of fair balance requirement to product websites). The FDA had not explicitly stated whether each individual page must contain a fair balance of use and risk information or whether the FDA will evaluate the entire website as a whole when deciding if there is a fair balance and a true statement. *Id.*

¹⁴⁷ See Stephanie Clifford, *FDA Rules on Drug Ads Sow Confusion as Applied to Web*, N.Y. TIMES, Apr. 16, 2009, at B7, available at <http://www.nytimes.com/2009/04/17/business/media/17adco.html> (discussing industry response to FDA Warning letters). Elizabeth Baxter, spokeswoman for Sanofi-Aventis, stated that the industry viewed the use of links as consistent with the regulations because the FDA has not issued guidelines about hyperlinks and the definition of a page. *Id.* As explained by Arnie Friede, counsel at the corporate law firm McDermott, Will & Emery, the industry believed “as long as pharmaceutical companies provided risk information within one click of their search ads — on the page that the ad linked to — they assumed they were in compliance.” *Id.*

¹⁴⁸ See Vicki W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of Approved Drugs: Why the False Claims Act is the Wrong Rx*, 12 J. HEALTH CARE L. & POL’Y 119, 127 (2009) (criticizing continued FDA and DOJ enforcement without judicial review of enforcement theories); see also U.S. Department of Justice, *Elan Pharmaceuticals Pleads Guilty, Sentenced for Off-Label Marketing of Zonegran* (Feb. 28, 2011), <http://www.justice.gov/usao/ma/news/2011/February/ElanSentencingPR.html> (describing settlement as “part of the government’s emphasis on combating health care fraud”). The focus on health care fraud has produced over nine billion dollars in recoveries. U.S. Department of Justice, *Pharmaceutical Manufacturers to Pay*

manufacturers citing sponsored links in violation of the FDCA.¹⁴⁹ The letters mandated that the companies' Google-sponsored advertisements had to include the use and risk information for each drug within each advertisement despite the limitations on characters imposed by Google.¹⁵⁰ Therefore, the manufacturers had misbranded the drugs because the advertisements made representations about the efficacy without communicating the associated risk and contraindication information.¹⁵¹ These letters

§421.2 Million to Settle False Claims Act Cases (Dec. 7, 2010), <http://www.justice.gov/opa/pr/2010/December/10-civ-1398.html>.

¹⁴⁹ See U.S. Food and Drug Administration, *Warning Letters 2009*, FDA.GOV, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm055773.htm> (last visited Jan. 17, 2012) (supplying copies of all FDA enforcement Warning letters). On April 3, 2009, the FDA sent Warning Letters to Eli Lilly, Hoffman-LaRoche, Merck, Boehringer Ingelheim Pharmaceuticals, Genentech, Novartis, Pfizer, Johnson & Johnson, Cephalon, Forest Laboratories, GlaxoSmithKline, Bayer, Sanofi-Aventis, and Biogen. *Id.*

¹⁵⁰ See, e.g., U.S. Food and Drug Administration, *Warning Letter to Eli Lilly and Co. Re: NDA #21-427, 21-733, 22-148 Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use NDA #20-815, 22-042 EVISTA (raloxifene hydrochloride) Tablets for Oral Use NDA #20-509 Gemzar (gemcitabine HCl) for Injection MACMIS ID #17320*, FDA.GOV (Apr. 3, 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM143536.pdf>; U.S. Food and Drug Administration, *Warning Letter to Hoffman-LaRoche Inc. Re: NDA #21-455, 21-858 BONIVA (ibandronate sodium) Tablets BLA #103964 PEGASYS (peginterferon alfa-2a) for Injection NDA #20-896 XELODA (capecitabine) Tablets MACMIS ID #17318*, FDA.GOV (Apr. 3, 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM143508.pdf>; U.S. Food and Drug Administration, *Warning Letter to Merck & Co., Inc. Re: NDA No. 21-995 JANUVLA™ (sitagliptin) Tablets NDA No. 20-788 PROPECLA (finasteride) Tablets NDA No. 20-829, 20-830, 21-409 SINGULAIR™ (montelukast sodium) granule; tablet, chewable; tablet, film coated NDA No. 21-549 EMEND (aprepitant) Capsules MACMIS ID # 17312*, FDA.GOV (Apr. 3, 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM143503.pdf>.

¹⁵¹ See *supra* note 150 and accompanying text. The ads made efficacy representations about the drugs but did not include any risk information. For example, one of the ads claimed "Rituxan (Rituximab) . . . Rituxan is FDA-approved to treat non-Hodgkin's lymphoma and RA. www.Rituxan.com " but made no representations about the associated side effects. U.S. Food and Drug Administration, *Warning Letter to Genentech, Inc. Re: BLA No. 125085 Avastin (Bevacizumab), BLA No. 125156 LUCENTIS™ (ranibizumab injection), BLA No. 103705, 103737 RITUXAN (rituximab), BLA No. 103976 Xolair (Omalizumab) For Subcutaneous Use, BLA No. 103792 HERCEPTIN (trastuzumab), BLA No. 103532 Pulmozyme (dornase alfa) Inhalation Solution MACMIS ID #17309*, FDA.GOV (Apr. 3, 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM143497.pdf>. The

clarified the FDA's position on the content requirements for Google-sponsored advertisements but did not address all other uses for hyperlinks.¹⁵²

IV. Breaking New Ground: The First FDA Action Targeting Social Media

The FDA recently clarified for the first time some regulatory issues regarding Internet marketing using social media.¹⁵³ On July 29, 2010, the Division of Drug Marketing, Advertising, and Communications ("DDMAC") sent a warning letter directing Novartis to stop marketing Tasigna with a "Facebook Share" media widget.¹⁵⁴ The Tasigna website contained a button that allowed users to post a statement on their personal Facebook page containing an image, a description of the drug, and a hyperlink to the Tasigna webpage.¹⁵⁵ Users could also share the content for Tasigna with other

advertisements presented uses and not risks, so there were no true statements about the drugs. *See id.* at 4-5. Therefore, the drugs were deemed misbranded. *Id.* at 5.

¹⁵² *See* McCubrey & Forgues, *supra* note 128, at 56-57 (suggesting next steps for FDA regulation); *see* Senger, *supra* note 138, at 219 (postulating potential topics for the FDA public hearing on Internet promotion); *see also* Letter from Thomas Abrams, Director, Division of Drug Marketing, Advertising, and Communications, to Fabio Gratton, Questions for the FDA Regarding "Next Steps" for Guidance Related to the Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools (Dec. 11, 2009), *available at* http://www.fdasm.com/docs/FINAL%20DDMAC%20Responses%20to%20FDASM_Questions.pdf. The regulations do not specifically address hyperlinks, but when questioned, the FDA stated "that the FDA never had what some are referring to as a 'one-click rule.'" *Id.*

¹⁵³ Dale Cooke, *Regulatory Alert: FDA's First Facebook Enforcement Action*, DIGITAS HEALTH (Aug. 4, 2010), http://www.cohealthcom.org/wp-content/uploads/2010/12/Digitas_Facebook_Alert_Aug2010.pdf ("Food and Drug Administration (FDA) has taken its first enforcement action against a pharmaceutical company for its use of Facebook."); *see* Smith et al., *supra* note 134, at 1 (describing Novartis warning letter as "the first enforcement action against a pharmaceutical company for its use of a social media sharing tool in marketing a prescription drug").

¹⁵⁴ *Warning Letter to Novartis Pharmaceuticals Corp. Re: NDA # 022068 Tasigna (nilotinib) Capsules MACMIS # 18870*, FDA.GOV (Jul. 29, 2010), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersToPharmaceuticalCompanies/UCM221325.pdf> [hereinafter *Novartis Warning Letter*]. The DDMAC specifically asked Novartis to "immediately cease the dissemination of violative promotional materials for Tasigna." *Id.* at 5. The FDA defined a "social media widget" as a way Facebook users to share articles, pages, video, or flash content of a site with other Facebook users. *Id.* Over two billion pieces of content are shared each week through Facebook. *Id.* With two clicks, visitors to a website can share any page of that website through Facebook by generating a link to the page, along with a thumbnail image and a brief description (i.e., "shared content") that will appear on the users' profiles and, depending on privacy settings, in the home page stream of all of the users' friends. *Id.* Each time a link is shared by one user, potentially hundreds of new people may see and/or click through on the link. *Id.* at 1 n.1.

¹⁵⁵ *See Novartis Warning Letter*, *supra* note 154, at 2. In addition to posting on their own Facebook

Facebook users via newsfeeds or wall postings.¹⁵⁶ Novartis created the content, and users were able to add additional comments but could not modify the advertisement that Novartis created.¹⁵⁷ In addition to Facebook widgets, the FDA explicitly expanded the scope of this warning letter to include other social media sharing applications because they all “raise similar issues.”¹⁵⁸

Novartis manufactures Tasigna, a cancer treatment used to treat a type of leukemia called Philadelphia chromosome-positive chronic myeloid leukemia (“Ph+ CML”) in adult patients who have become resistant to other treatments.¹⁵⁹ The effectiveness of Tasigna is limited “based on hematologic and cytogenetic response rates” in different patients, and there are no controlled studies showing “improvement in disease-related symptoms or increased survival rate” after using Tasigna.¹⁶⁰ The FDA-approved Tasigna labeling outlines several serious risks in the Boxed Warning, Contraindications, Warnings and Precautions, and Adverse Reactions sections.¹⁶¹ The risks include: QT prolongation (a possibly life-threatening heart condition) and sudden deaths; severe myelosuppression (a decrease in the ability of bone marrow to produce blood cells and a common side effect of chemotherapy); elevated serum lipase (an increase in enzymes associated with pancreatitis and other digestive disorders); liver function abnormalities; electrolyte abnormalities; and liver impairment.¹⁶² Patients must

walls, users were able to send the advertising “separately as a message to other specified Facebook users.” *Id.*

¹⁵⁶ See *Novartis Warning Letter*, *supra* note 154, at 2. The FDA explained that the widget “allows users to post the shared content for Tasigna on their Facebook profile walls and to share this same information with other Facebook users (i.e., the user’s Friends, Friends of Friends, or Everyone) via newsfeeds or wall postings.” *Id.*

¹⁵⁷ *Novartis Warning Letter*, *supra* note 154, at 1 n.2. The FDA explicitly stated that they were concerned with manufacturer-generated content and not with user generated claims about the drug. *Id.* None of the citations included user generated comments. *Id.* at 2-5.

¹⁵⁸ *Novartis Warning Letter*, *supra* note 154, at 1 n.3 (including other social media “Share” applications in the scope of the warning letter). The “Share this” tool allows people to post links to programs like Facebook, Twitter, Google, or Yahoo! with just one click. *Id.*

¹⁵⁹ *Highlights of Prescribing Information for Tasigna*, FDA.GOV, 2 (Aug. 2009), http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022068s002lbl.pdf [hereinafter *Tasigna Approved Labeling*]. The FDA approved Tasigna for “[t]reatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase” and “[t]reatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib.” *Id.*

¹⁶⁰ See *Tasigna Approved Labeling*, *supra* note 159, at 4.

¹⁶¹ See *Tasigna Approved Labeling*, *supra* note 159, at 2.

¹⁶² See *Tasigna Approved Labeling*, *supra* note 159, at 2. ¹⁵⁹The serious side effects include:

[F]eeling lightheaded, fainting, or having an irregular heartbeat, unexplained bleeding or bruising, blood in urine or stool, unexplained weakness, yellow

be closely monitored when using Tasigna, and the risks are so severe that the FDA required a Risk Evaluation and Mitigation Strategy (“REMS”) for Tasigna to educate physicians and patients about the risks of the drug and proper dosing strategies to mitigate serious adverse events.¹⁶³

The letter cited Novartis for four violations: omission of risk; broadening of indication; unsubstantiated superiority claims/overstatement of efficacy; and failure to submit “specimens of any labeling or advertising devised for promotion of a drug product.”¹⁶⁴ Some of the shared content did not have a fair balance of risk and use information because the postings made efficacy claims, but failed to state any risk information whatsoever.¹⁶⁵ For example, one advertisement was titled “Home – Tasigna (nilotinib) 200 mg capsules” and the text stated “<http://www.us.tasigna.com> Tasigna (nilotinib) is used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML).”¹⁶⁶ Aware that Novartis had included hyperlinks

skin and eyes, shortness of breath, sudden stomach area pain with nausea and vomiting, sudden headache, changes in your eyesight, not being aware of what is going on around you, and becoming unconscious.

Id. at 20-21. The most commonly reported adverse reactions are “rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia.” *Id.* at 9. Tasigna should not be taken by “patients with hypokalemia, hypomagnesemia, or long QT syndrome.” *Id.* at 2.

¹⁶³ See *Tasigna Approved Labeling*, *supra* note 159, at 18 (supplying patient counseling information). Patients should take an electrocardiogram before starting, seven days after starting, and regularly while taking Tasigna. *Id.* Physicians should also test blood cell levels (including red, white and platelet counts), electrolyte levels (potassium and magnesium), pancreas and liver functioning, and take bone marrow samples. *Id.* at 20. In addition to laboratory monitoring, physicians should tell patients about several drug and food interactions. *Id.* Grapefruit and supplements, such as St. John’s Wort, interact negatively with Tasigna. *Id.*

¹⁶⁴ *Novartis Warning Letter*, *supra* note 154, at 2-5. The DDMAC deemed Novartis to have misbranded Tasigna as a result of these violations. *Id.* at 1.

¹⁶⁵ *Novartis Warning Letter*, *supra* note 154, at 3 (stating that “[p]osted shared content available from several of the Tasigna product web pages makes representations or suggestions about the efficacy of Tasigna, but fails to communicate any risk information.”). The advertisement was misleading because the lack of risk information “suggests that Tasigna is safer than has been demonstrated by substantial evidence or substantial clinical experience.” *Id.* For Tasigna specifically, the FDA was “particularly concern[ed]” about the omission of risk information because the drug is so dangerous and has so many severe risks. *Id.*

¹⁶⁶ *Novartis Warning Letter*, *supra* note 154, at 3. The FDA posted another example showing “Treating Your Ph+ CML with Tasigna | Tasigna (nilotinib) 200-mg capsules, www.us.tasigna.com, In addition to taking Tasigna (nilotinib) 200-mg capsules, talking to your doctor and receiving health tips can help you treat your CML.” *Id.*

to the risk information in the shared content, the FDA made it clear that hyperlinking to the risk information did not adequately communicate the risks, and, therefore, the advertisement was untruthful and misleading.¹⁶⁷

Novartis misleadingly broadened the indication of Tasigna by implying that Tasigna is approved for all Ph+ CML patients even though the approval is for a more limited group of patients.¹⁶⁸ Shared content such as “Treating Your Ph+ CML with Tasigna | Tasigna (nilotinib) 200-mg capsules, www.us.tasigna.com, In addition to taking Tasigna (nilotinib) 200-mg capsules, talking to your doctor and receiving health tips can help you treat your CML” implied that Tasigna is approved for all patients with Ph+ CML when it has only been approved for patients with chronic or accelerated cancer who have already tried other options.¹⁶⁹ Novartis overstated the efficacy of the drug in postings such as “CML (Chronic Myeloid Leukemia) Treatment – Find out if Tasigna is Right for You, www.us.tasigna.com, Tasigna (nilotinib) 200-mg capsules from Novartis is a next-generation treatment for Ph+ Chronic Myeloid Leukemia in adult patients in chronic or accelerated phase who are resistant to Gleevec.”¹⁷⁰ Tasigna’s advantage over other treatments has never been demonstrated by substantial evidence or substantial clinical experience, and the phrase “next-generation” treatment “misleadingly suggests superiority.”¹⁷¹ Although Novartis had submitted some website content to the FDA for approval, they had not submitted the shared content to the FDA, and failed to comply with the regulations.¹⁷²

¹⁶⁷ *Novartis Warning Letter*, *supra* note 154, at 3.

¹⁶⁸ *Novartis Warning Letter*, *supra* note 154, at 3 (citing Novartis for several instances of broadening the indication).

¹⁶⁹ *Novartis Warning Letter*, *supra* note 154, at 3. At the time, the FDA had only approved Tasigna as “a second-line option after failure or intolerance to prior therapy that included imatinib.” *Id.* Conversely, Tasigna was not approved as a first-line therapy at the time. *Id.* at 4. Since the warning letter, Tasigna has been approved for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase who have tried other therapies, but Tasigna is still not approved for all Ph+ CML patients. *Id.*

¹⁷⁰ *Novartis Warning Letter*, *supra* note 154, at 4.

¹⁷¹ *Novartis Warning Letter*, *supra* note 154, at 4. Not only has the FDA warned Novartis about using the phrase “next-generation,” they “previously provided written advisory comments to Novartis about the misleading implications of the phrase ‘next generation’ when referring to Tasigna” specifically. *Id.* at 5.

¹⁷² *Novartis Warning Letter*, *supra* note 154, at 5. The FDA requires all advertising content to be submitted for approval at least thirty days before introducing it to the public or physicians. 21 C.F.R. § 314.550 (2010). Manufacturers must submit a completed transmittal Form FDA-2253 with the advertising content and all labeling. *Id.* Novartis violated these regulations because they did not adhere to the required regulatory procedure. *See Novartis Warning Letter*, *supra* note 154, at 5.

V. A Plea for Rules and Expectations

The Novartis notice-of-violation letter clarifies some FDA expectations for using social media to promote prescription pharmaceutical drugs.¹⁷³ The FDA did not prohibit the use of social media *per se*, so long as advertisements comport with existing content regulations.¹⁷⁴ The “one-click” rule is dead, and manufacturers are on notice that all drug advertisements, regardless of the technology or tool, must include use and risk information.¹⁷⁵ The use of hyperlinks is insufficient to meet the fair balance requirement, and Internet shared content that does not present a fair balance of efficacy statements and risk information may be considered misbranded.¹⁷⁶ This expectation applies to all social media technology, including microblogs like Twitter, regardless of limits on the number of characters that can be used for each advertisement.¹⁷⁷ Additionally, it is important that pharmaceutical manufacturers understand how Internet tools and technology work because they will be responsible for submitting all content, in all forms, to the FDA for approval.¹⁷⁸

Despite providing some clarification, the case-by-case enforcement approach utilized by the FDA has left many questions unanswered.¹⁷⁹ Although the FDA made it clear that risk information must accompany any efficacy statements, it did not mandate what level of disclosure would be satisfactory: full product labeling; the brief summary; or the major statement.¹⁸⁰ The risks for Tassigna are extremely high, and it is unclear

¹⁷³ See Cooke, *supra* note 153, at 1 (analyzing FDA policy stemming from Novartis warning letter).

¹⁷⁴ See generally *Novartis Warning Letter*, *supra* note 154; see also Smith et al., *supra* note 134, at 4 (“[t]he FDA did not prohibit the use of social media tools or media to promote drugs”). The FDA only criticized the content of the Novartis shared content. *Id.* They never prohibited using social media to promote pharmaceutical drugs. *Id.*

¹⁷⁵ See *Novartis Warning Letter*, *supra* note 154, at 2 (requiring Internet advertisements to include risk and use information for all social media “share” technology).

¹⁷⁶ See *supra* notes 166 and 167 and accompanying text.

¹⁷⁷ See *supra* note 158 and accompanying text.

¹⁷⁸ See Combs, *supra* note 7, at 2 (presenting implications of Novartis warning letter); Smith et al., *supra* note 134, at 3-4 (summarizing the Novartis warning letter). Pharmaceutical manufacturers must “understand exactly how sharing tools and search engines function, how content will be developed, how meta tags may be used, and the form in which the content will ultimately be disseminated” because the DDMAC will monitor all metadata/shared content. *Id.* at 4.

¹⁷⁹ See Cooke, *supra* note 153, at 1 (“[t]his single enforcement action does NOT answer all of the questions raised during the social media hearings or about the use of social media in general”); Smith et al., *supra* note 134, at 3 (“the Novartis notice-of-violation letter partially clarifies the FDA’s viewpoint on drug product promotion in the context of social sharing”); Combs, *supra* note 7, at 2 (“the implications of DDMAC’s statements are not entirely clear”).

¹⁸⁰ See Cooke, *supra* note 153, at 2 (noting that the Novartis warning letter’s lack of specificity in

whether the FDA would scrutinize an advertisement for a drug with lower risks to the same degree, because it is easier to make a true and balanced statement about a drug's safety and efficacy if the risks are lower.¹⁸¹ Additionally, other forms of social media are so complicated and different from a "Facebook Share" widget that the Novartis letter cannot provide a meaningful source of guidance going forward.¹⁸²

The FDA should issue a legislative rule through the notice-and-comment process that not only legally binds pharmaceutical manufacturers to clear advertising expectations, but also grants the public a meaningful chance to provide the FDA with input about the rule.¹⁸³ The FDA is implementing new policy expectations without any veil of legal enforceability because the agency is implementing and developing agency policy on a case by case basis rather than by agency rulemaking.¹⁸⁴ At a minimum, the FDA should issue a Level 1 guidance document because Internet marketing is "highly controversial" and the FDA is making policy determinations in otherwise unregulated areas.¹⁸⁵ Even though the FDA solicited and gathered public input in 1996 and 2009, it has not responded publicly and directly to all of the issues that were highlighted in the

its discussion of risk disclosure). The FDA may be leaning towards a major statement requirement, like that required for broadcast advertising. *Id.* at 2. Like print media, it would be easy to include the full product label for some types of Internet marketing, but such a requirement would functionally prohibit manufacturers from using social media with limited space. *See* Combs, *supra* note 7, at 2; *see also supra* note 120 and accompanying text (describing the "major statement").

¹⁸¹ *See* Combs, *supra* note 7, at 2 (noting that it is unclear whether the DDMAC would apply a lower standard of scrutiny to drugs with fewer risks).

¹⁸² *See* Combs, *supra* note 7, at 2 (discussing the difficulties of universally applying rules regulating social media). Other problems include: "the anonymous, 'public' nature of comments in chat rooms and message boards; the different characteristics of sites and tools (e.g., Wikipedia, Facebook, Twitter, YouTube); the difficulty of monitoring real-time communication; the sheer volume of possible communication outlets and third-party posts; and the global nature of sites and tools." *Id.*

¹⁸³ *See supra* notes 21-24 and accompanying text (describing the role of the public in the process of the legislative notice-and-comment process).

¹⁸⁴ *See supra* notes 18-20 and accompanying text; *see also* Combs, *supra* note 7, at 2 (criticizing case-by-case enforcement because each case is never "comprehensive enough to guide companies in their design of promotional strategies and attempts to comply with the law").

¹⁸⁵ *See* 21 C.F.R. § 10.115(c)(1)(iv) (2010); *see also supra* note 31 (explaining regulation directing FDA to promulgate Level 1 Guidance Document when addressing "highly controversial" issues); Combs, *supra* note 7, at 2 (urging the FDA to "issue guidance in this area not only to provide companies with certainty as they develop their advertising strategies, but also to ensure that the information available to consumers is truthful, non-misleading, and fairly balanced, regardless of the form of media used to convey the message"); *supra* notes 31-32 and accompanying text (describing the process for issuing Level 1 documents).

hearings.¹⁸⁶ Individual enforcement actions deny the public the opportunity to be heard in a meaningful way because the FDA never has to respond to the public concerns.¹⁸⁷ Rather than waiting until Internet marketing causes some sort of public health crisis, as the FDA has done in the past before promulgating new rules, the FDA should put a strong regulatory scheme in place that incorporates the public agenda and addresses all forms of Internet marketing.¹⁸⁸ Until that day, pharmaceutical manufacturers must promote their products subject to current regulations that are unclear at best, and completely inapplicable at worst.¹⁸⁹

VI. Conclusion

During the first half of the twentieth century, Congress created the FDA to protect public health and safety and, over time, expanded the scope and breadth of the FDA's regulatory authority. The FDA assumed the role as the sole guardian of public health while trying to maintain balance between the competing interests of pharmaceutical manufacturers and consumers. A century later, in a generally more competitive and risk averse climate, the drug approval process is a tightly regulated, staggeringly time-consuming, and overwhelmingly expensive process. Concerns about safety and efficacy have led to an ever-increasing focus on pharmaceutical marketing. At the same time, pharmaceutical manufacturers have been given great leeway when it comes to DTC marketing, and drug advertisements inundate consumers on a daily basis.

Despite multiple public hearings, the FDA has been slow to address pharmaceutical Internet marketing. Thus far, the FDA has expressed their policy through case-by-case enforcement actions, limited to the specific facts of the situation, rather than promulgating guidance documents or agency rules addressing Internet marketing as a whole. The Internet is here to stay, modes of Internet marketing are only becoming more numerous, and manufacturers have been chomping at the bit to use social media to market their products. The Novartis warning letter provided some guidance and ended the debate about the use of hyperlinks, but several issues are still up in the air because the scope of the letter was limited to social media share widgets. The

¹⁸⁶ See *supra* notes 130-133 and accompanying text (describing the hearings).

¹⁸⁷ See *supra* notes 23-24 and accompanying text (explaining why public participation is beneficial). Individual enforcement allows the FDA to avoid public notice-and-comment procedures because the FDA is not issuing a rule. See *supra* note 12 and accompanying text (discussing the process for promulgating rules).

¹⁸⁸ See *supra* notes 44, 53-55 and accompanying text.

¹⁸⁹ See *supra* notes 178-182 and accompanying text (noting the lack of clarity in the current regulations).

lack of guidance leaves manufacturers confused, and puts the public in harm's way because manufacturers will push the limits until they are reigned in. As the primary authority, the FDA should step up to the plate, issue an agency rule, and legally bind pharmaceutical manufacturers' advertising within clearly defined parameters.