

January 2017

Memorandum

**Public Health Interests and First Amendment Considerations
Related to Manufacturer Communications Regarding
Unapproved Uses of Approved or Cleared Medical Products**

Glossary

This document discusses manufacturer communications regarding unapproved uses of approved or cleared human drugs and medical devices, including biological products, and animal drugs in nonfood producing animals. As described in Appendix A, there are some distinctions in the review processes for these different types of medical products that ultimately permit firms to market the products. In discussing these products together, this document uses several general terms,¹ which are as follows:

Approved/cleared medical product; approval/clearance	Approved/cleared medical product refers to a medical product intended for human use that may be legally introduced into interstate commerce for at least one use under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act as a result of having satisfied applicable premarket review requirements. It also refers to an approved animal or human drug that can legally be used in an extralabel use manner in animals, pursuant to sections 512(a)(4) or (5) of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 530. It also refers to devices that are exempt from premarket notification. Approval/clearance refers to the satisfaction of the applicable premarket review requirements.
Approved/cleared use	This term refers to an intended use in the labeling approved by FDA, an intended use included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that falls within an exemption from clearance under section 510 of the Federal Food, Drug, and Cosmetic Act.
Device	This term refers to a medical device intended for human use, including a device that is licensed as a biological product.
Drug	This term refers to a human drug, including a drug that is licensed as a biological product, and an animal drug that may legally be used in an extra-label manner in animals, pursuant to sections 512(a)(4) or (5) of the Federal Food, Drug, and Cosmetic, and 21 C.F.R. § 530.
FDA or Agency	This acronym or term refers to the Food and Drug Administration.
FDA Authorities	This term refers to the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, as well as implementing regulations.
Firms	This term refers to medical product manufacturers, packers, and distributors and all their representatives, including both corporate entities and natural individuals.
Health care providers	This term refers to individuals such as physicians, veterinarians, dentists, physician assistants, nurse practitioners, or registered nurses who are licensed or otherwise authorized by the state to administer or use medical products.
Medical products	This term refers to both drugs and devices.

¹ The descriptions in this table and in the Summary of Statutory and Regulatory Authority below are not intended to reflect a complete and detailed recitation of the relevant legal authority. Appendix A contains a more complete discussion of the relevant statutory provisions and implementing regulations.

<p>Premarket review</p>	<p>This term refers to FDA’s review of scientific evidence regarding a medical product to evaluate whether it satisfies requirements for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act that enable a medical product to be legally introduced into interstate commerce for a specified intended use. For devices, the term encompasses FDA’s classification of a device type (including <i>de novo</i> classification) as well as review of premarket approval applications (PMA) and premarket notifications (510(k)).</p>
<p>Unapproved use</p>	<p>This term refers to an intended use that is not included in the labeling approved by FDA, an intended use that is not included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that does not fall within an exemption from clearance under section 510 of the Federal Food, Drug, and Cosmetic Act.</p>

1 **I. INTRODUCTION**

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3 The Agency is engaged in a reexamination of its rules and policies relating to firm
4 communications regarding unapproved uses of approved/cleared medical products, with the goal
5 of determining how best to integrate the significant and sometimes competing public health and
6 safety interests served by FDA’s regulatory approach related to unapproved uses of medical
7 products with ongoing developments in science and technology, medicine, health care delivery,
8 and constitutional law. To that end, FDA held a two-day public hearing on November 9-10,
9 2016, to obtain input on these issues, and created a docket for the submission of written
10 comments. FDA is grateful to all of the speakers at the hearing for their thoughtful
11 presentations.

12
13 At the public hearing, a number of speakers presented legal views regarding the application of
14 First Amendment principles to firm communications regarding unapproved uses of
15 approved/cleared medical products. Some expressed the view that FDA had not sufficiently
16 discussed the First Amendment in the notice of the public hearing. FDA is now placing this
17 Memorandum in the docket for the public hearing to provide additional background and seek
18 input on the full range of issues to consider as part of its reexamination, including First
19 Amendment considerations. FDA is seeking comment on the public health and safety interests
20 advanced by the FDA Authorities, many of which are discussed in this document, as well as
21 comment on what approaches could integrate and advance these sometimes competing public
22 health and safety interests with First Amendment jurisprudence.

23
24 **II. SUMMARY OF STATUTORY AND REGULATORY AUTHORITY**

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26 The FDA Authorities prohibit the introduction (or causing the introduction) into interstate
27 commerce of a medical product that fails to comply with applicable requirements for approval,
28 licensing, or clearance, or is otherwise misbranded or adulterated.² This prohibition includes
29 introducing (or causing the introduction) into interstate commerce a medical product that is
30 intended for a use that has not been approved or cleared by FDA, even if that same product is
31 approved or cleared for a different use.

32
33 Congress developed the premarket review frameworks for medical products in response to public
34 health tragedies, realizing that: (1) safety and effectiveness need to be appropriately studied by
35 firms and then independently evaluated for each intended use because the evidence that
36 demonstrates effectiveness and safety for one use of a product provides no guarantee of the
37 effectiveness or safety of additional uses; and (2) exclusive reliance on post-market remedies,
38 such as enforcement actions for false or misleading labeling, is inadequate because it does not
39 prevent consumers from experiencing harm from unsafe and/or ineffective treatments.

40
41 The concept of intended use is fundamental to the regulatory approach embodied in the FDA
42 Authorities. Intended use is an element in the definitions of drug and device and thus helps

² See *supra* note 1.

43 define the scope of FDA’s jurisdiction over medical products.³ For example, charcoal is the key
44 ingredient in common products sold as fuel, a use outside FDA’s jurisdiction, but charcoal
45 products are drugs when intended for emergency treatment of poisoning by ingestion. Thus, it is
46 the intended use to treat poisoning that is key to distinguishing a product that might be sold to
47 fuel a fire from a drug subject to the FDA Authorities. In addition to establishing a threshold
48 element that makes the product subject to the drug or device provisions of the FDA Authorities,
49 intended use may affect the appropriate premarket review pathway for a device and also is a
50 separate element in establishing certain violations under the FDA Authorities.

51
52 For both drugs and devices, the intended use of a product can be established from its label,
53 accompanying labeling, promotional claims, advertising, and any other relevant source.⁴ As the
54 legislative history of the Federal Food, Drug, and Cosmetic Act (FD&C Act) reflects, “[t]he
55 manufacturer of the article, through his representations in connection with its sale, can determine
56 the use to which the article is to be put.”⁵ Accordingly, a firm’s communications are relevant to
57 establishing whether its product is subject to the FDA Authorities.

58
59 FDA’s regulatory authority extends to the labeling and certain advertising of medical products,
60 which again involve firm communications. This type of regulatory framework is not unique to
61 FDA’s regulation of medical products – numerous Federal and state agencies regulate the
62 conduct of particular industries, including the content of their commercial communications.⁶

63
64 While there are distinctions in the review frameworks for different types of medical products,⁷ as
65 a general matter, FDA considers the benefit-risk profile of the product for each intended use
66 during the premarket review process. In that process, FDA considers whether the established
67 health benefits of the product for a particular use outweigh the identified risks of the product.
68 The separate weighing of benefit and risk for each intended use is critical because evidence
69 establishing effectiveness in one setting (e.g., for a particular disease or when a specified dosage
70 is used) does not establish effectiveness of the same product in another setting (e.g., for a

³ 21 U.S.C. §§ 321(g)(1)(B)-(C) and (h)(2)-(3); *see also* *United States v. Caronia*, 703 F.3d 149, 170-71 (2d Cir. 2012) (Livingston, J. dissenting).

⁴ *See, e.g.*, *United States v. Storage Spaces Designated Nos. “8” & “49”*, 777 F.2d 1363, 1366 (9th Cir. 1985); *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980). Intended use can be established not only by the firm’s subjective claims of intent, but also by objective evidence, which may include a variety of direct and circumstantial evidence. 21 C.F.R. §§ 201.128 and 801.4.

⁵ *See* *United States v. An Article ... Sudden Change*, 409 F.2d 734, 739 (2d Cir. 1969) (quoting S. REP. NO. 361, 74 Cong., 1st Sess.).

⁶ *See* *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 585-92 (2011) (Breyer, J., dissenting) (discussing examples of regulatory authority related to the content of communications of particular industries); *see also* Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 549-50 (2014) (“This pattern in the law - using intent as the predicate for regulation and then using speech as evidence of intent - is quite common, and not peculiar to pharmaceutical regulation. As early as 1888, the Supreme Court affirmed a state court criminal conviction for someone who manufactured an ‘oleaginous substance’ otherwise perfectly legal, except that he intended for it to be used as food, and thereby his manufacture of it fell under the purview of a state regulator. Similarly, a hollow piece of glass with a bowl on the end is illegal drug paraphernalia only if intended for such illicit uses. An automobile is not subject to regulation by the Federal Aviation Administration, unless it is ‘intended to be used for flight in the air.’”) (citations omitted).

⁷ *See* Appendix A.

71 different disease or when a different dosage is used). Similarly, a product considered safe in one
72 setting might not be considered safe in another setting. Despite the distinctions in the legal
73 frameworks and associated differences in premarket review pathways and processes, underlying
74 them all are the goals of spurring innovation based on reliable scientific evidence of
75 effectiveness and of ensuring the safety and effectiveness of medical products for each intended
76 use.

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78 **III. PUBLIC HEALTH INTERESTS RELATED TO FIRM COMMUNICATIONS**
79 **REGARDING UNAPPROVED USES OF APPROVED/CLEARED MEDICAL**
80 **PRODUCTS AND MEASURES THAT ADVANCE THESE INTERESTS**

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82 Firm communications regarding unapproved uses of approved/cleared medical products
83 implicate several substantial government interests related to health and safety. Among these are
84 motivating the development of robust scientific data on safety and efficacy; maintaining the
85 premarket review process for safety and efficacy of each intended use in order to prevent harm,
86 protect against fraud, misrepresentation, and bias, and to prevent the diversion of health care
87 resources toward ineffective treatments; ensuring required labeling is accurate and informative;
88 protecting the integrity and reliability of promotional information regarding medical product
89 uses; protecting human subjects receiving experimental treatments; ensuring informed consent;
90 maintaining incentives for clinical trial participation; protecting innovation incentives, including
91 statutory grants of exclusivity; promoting the development of products for underserved patients;
92 supporting informed decision-making for patient treatment; and furthering scientific
93 understanding and research. All of these interests relate to FDA's larger substantial interest in
94 protecting and promoting public health.

95
96 The FDA Authorities, among other things, motivate the development of scientific evidence that
97 enables the reliable, population-level determination of the safety and efficacy of medical
98 products for each intended use; require that the evidence be developed and independently
99 reviewed before the products are marketed to the general public for each intended use; and
100 require that the product bears labeling that identifies each approved or cleared use of the product
101 and provides information for using the product safely and effectively for that approved or cleared
102 use for patients. At the same time, health care providers prescribe and use approved/cleared
103 medical products for unapproved uses when they judge that the unapproved use is medically
104 appropriate for their patients. Scientific or medical information regarding unapproved uses of
105 products may help health care providers make better decisions regarding a patient, such as where
106 the patient has a disease for which there is no approved/cleared treatment, where the patient is
107 part of a population that has not been studied, or where all approved/cleared treatments have
108 been exhausted. However, the use of approved/cleared medical products for unapproved uses
109 has also been associated with harm to patients, fraud, and waste of health care resources.

110
111 Integrating the many substantial interests, some of which are in tension with each other, in a way
112 that best promotes public health and comports with recent First Amendment jurisprudence is a
113 complex task. Because of the importance of these and the other interests discussed below, we
114 are making this Memorandum available for comment to help advance the dialogue about these
115 issues. To assist in that discussion, this section identifies many of these substantial interests.

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A. How the FDA Authorities Advance Public or Individual Health Interests

1. Motivating the Development of Robust Scientific Data on Safety and Efficacy

Congress mandated that firms gather data from rigorous scientific studies for each new use of a medical product by establishing scientific evidentiary thresholds for premarket review and approval/clearance. This mandate developed over time, in large part in response to conduct by firms that led to public health tragedies and insufficiency of previous regulatory authority to prevent the harm from occurring.⁸ In enacting the 1962 Kefauver-Harris Amendments to the FD&C Act (which first introduced an explicit efficacy requirement for drugs), Congress recognized that poorly conducted studies and anecdotal evidence from clinical practice do not provide adequate scientific information to conduct the drug risk/benefit assessments that are necessary to protect and promote public health.⁹ Due to similar concerns about unsafe and ineffective marketed devices, Congress enacted the Medical Device Amendments of 1976, which established a comprehensive scheme for the premarket and postmarket regulation of devices.¹⁰

The current premarket review processes for each new use of a medical product under the FDA Authorities require firms to generate the kind of data that supports a reliable conclusion that the reported results, particularly with regard to benefits (i.e., effectiveness), are caused by the use of the drug or device, and not a result of other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. These evidentiary requirements are also designed to motivate research to spur innovation based on reliable scientific evidence and to prevent harm.¹¹

⁸ For example, the Food, Drug, and Cosmetic Act of 1938, which introduced the requirement that firms demonstrate a drug product to be safe before being marketed, followed the deaths of approximately 100 people from ingesting “Elixir Sulfanilamide,” in which the lethal substance diethylene glycol was used as a solvent. There were no premarketing requirements that mandated that the firm test its product’s safety. Similarly, the passage of the Kefauver-Harris Amendments was precipitated in part by the distribution of thalidomide, a sleeping pill that caused birth defects when taken by pregnant women. See Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation and Labeling*, 36 FOOD DRUG COSM. L.J. 420 (1981). Significant problems with medical devices likewise preceded the Medical Device Amendments of 1976, including significant defects in cardiac pacemakers that led to 34 voluntary recalls involving 23,000 units, and serious side effects following implantation of intraocular lenses, including serious impairment of vision and the need to remove the eyes of some patients (H.R. REP. NO. 94-853, at 8 (1976)).

⁹ See *Cooper Labs., Inc. v. FDA*, 501 F.2d 772, 778 (D.C. Cir. 1974); see also *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619 (1973) (“The hearings underlying the 1962 Act [the Kefauver-Harris amendments to the FD&C Act] show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous.”).

¹⁰ For congressional history regarding the need for the Medical Device Amendments of 1976, see S. REP. NO. 94-33, at 2-6 (1975) and H.R. REP. NO. 94-853, at 5-12 (1976).

¹¹ See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 347 (2007) (“[D]rug regulation has come to play” an “important structural role” of “promoting a valuable form of pharmaceutical innovation - the development of credible information about the effects of drugs.”); Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 560-61 (2014) (The FD&C Act “provide[s] and protect[s] an epistemic and economic process of research and discovery, one that helps physicians make more rational decisions.”) (citations omitted); Tewodros Egualé et al., *Comment & Response: In Reply to In Defense of Off-label Prescribing*, 176 JAMA INTERN MED. 861-62 (June 2016) (Premarket review under the FDA Authorities “is exactly what produces

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141 Developing scientific information sufficient to establish safety and effectiveness for new uses of
142 medical products remains critically important because there are harms that have been associated
143 with the use of medical products for unapproved uses – harms to health, as well as fraud and the
144 diversion of limited resources to ineffective treatments.¹² When rigorous studies appropriately
145 designed to evaluate a new use have not been completed and subjected to FDA’s independent
146 scientific review, there is uncertainty about both effectiveness and safety for a particular
147 unapproved use. In late 2015, researchers announced the results of a large study of the incidence
148 of adverse drug events associated with unapproved uses of approved drugs. The study found the
149 risk of adverse events was higher for unapproved uses than for approved uses, and even higher
150 when the unapproved use was not supported by reliable scientific data.¹³ And, as the examples
151 described in Appendix B illustrate, experience has shown that even widespread acceptance of an
152 unapproved use in the medical community is not a guarantee that the medical product is safe or
153 effective for that use.

154
155 However, to conduct rigorous clinical research that can identify a benefit caused by a medical
156 product (and not a result of other influences, such as spontaneous change in the course of the
157 disease, placebo effect, or biased observation), firms must invest time and resources. Many of
158 the incentives to sponsor such research are likely to be diminished once products have been
159 approved/cleared for at least one use and can then be legally placed into widespread distribution.
160 The legal requirement to generate appropriate evidence to demonstrate the safety and
161 effectiveness of medical products for each intended use creates the impetus for firms to conduct
162 those studies for subsequent uses of products – studies that no other actor will likely have the
163 motivation and resources to undertake. If firms can promote general public use of unevaluated
164 uses, there may be greater potential for wide-scale public health tragedies, wasted public and
165 private health care dollars, and fraud.¹⁴

the scientific evidence that physicians need to prescribe appropriately.”).

¹² See, e.g., Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016) (summarizing study across cohort of 46,000 patients, and concluding that unapproved use of prescription drugs is associated with adverse drugs events, particularly where those uses lack strong scientific evidence in the form of at least one randomized controlled trial); Chester B. Good & Walid F. Gellad, *Off-Label Drug Use and Adverse Events, Turning up the Heat on Off-Label Prescribing*, 176 JAMA INTERN MED. 63-64 (Jan. 2016) (discussing reports of harm from unapproved uses of drugs); Aaron S. Kesselheim et al., *Mandatory Disclaimers On Dietary Supplements Do Not Reliably Communicate The Intended Issues*, 34 HEALTH AFFAIRS 438-46 (2015) (“Off-label drug prescribing has led to poor efficacy or harm in many instances in recent years, such as the use of nesiritide (Natrecor) for stable congestive heart failure, paroxetine (Paxil) for depression in children, antipsychotic drugs in elderly patients with dementia, and anti-epileptic medications for certain mood disorders. In each of these cases, patients were harmed by unsafe or ineffective off-label prescription drug use, which led to litigation. Manufacturers’ promotional practices were found to have encouraged these off-label uses.”) (citations omitted).

¹³ See Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016).

¹⁴ See Aaron S. Kesselheim & Michelle M. Mello, *Healthcare Decisions in the New Era of Healthcare Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1585 (2014) (“There [would] be no need for companies to design these studies to meet the FDA’s standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use but rather intend to use the study findings only in marketing communications. Companies [could] design studies in ways that maximize the chances of obtaining a desired result and select which studies to

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167 **2. Preventing Harm to Members of the Public; Protecting Against Fraud,**
168 **Misrepresentation and Bias; and Preventing the Diversion of Limited Health Care**
169 **Resources Toward Ineffective Treatments**
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171 Given the harms associated with the use of medical products, Congress determined that FDA
172 must review the safety and effectiveness of each intended use of certain medical products before
173 the product is marketed for that use. This requirement serves at least three distinct but
174 interrelated government interests: preventing harm to members of the public; protecting against
175 fraud, misrepresentation, and bias; and preventing the diversion of health care resources toward
176 ineffective treatments. The discussion below explains how the premarket review requirement
177 advances these interests.
178

179 a. Timing of Review to Prevent Harm. Premarket review of safety and
180 effectiveness is a very effective way to protect the public from harm; post-market remedies are
181 often taken only after harm has occurred, and thus such remedies do not provide an equivalent
182 level of protection. The harms premarket review protects against include:
183

- 184 • Direct harms to health. Many medical products have significant adverse side effects, and
185 therefore may be deemed safe by FDA only with respect to particular uses that involve
186 significant countervailing benefits.
- 187 • Indirect harms to health. Medical products that are ineffective cause indirect harm,
188 including the lost opportunity to select an effective intervention against underlying
189 disease (or the delayed diagnosis of a disease or condition in the context of diagnostic
190 products), which is a harm that often cannot be fully remedied after it is incurred.¹⁵ This
191 also leads to a waste of health care resources.
192

193 The history of drug product regulation before 1962 demonstrates that exclusive reliance on post-
194 marketing remedies, such as enforcement actions for false or misleading labeling, was
195 inadequate to protect the public health. Those post-market remedies were not sufficient to deter
196 some firms from making unsubstantiated or misleading claims to encourage use of their products
197 and therefore could not prevent the often serious harm to health caused by the use of these
198 products. Premarket approval for each intended use was necessary to prevent some firms from
199 obtaining approval for one use, then promoting the drug for other, unapproved uses without first
200 demonstrating through the approval process that the drug was safe and effective for each new
201 use.¹⁶ Likewise, premarket review of medical devices was a key feature of the Medical Device

emphasize in promotional communications, ignoring others that do not support their promotional message.”);
Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427,
1427-28 (2008) (Encouraging unapproved uses “undermines the incentives for manufacturers to perform rigorous
studies — and instead subtly encourages them to game the system by seeking approval for secondary indications for
which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based
practice.”).

¹⁵ See Declaration of Robert Temple, MD, Allergan, Inc. v. United States, 1:09-cv-01879 (D.D.C. Dec. 11, 2009).

¹⁶ See S. REP. NO. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (if firms were not required to
demonstrate safety and effectiveness for new uses, “[t]he expectation would be that the initial claims would tend to
be quite limited,” and “[t]hereafter ‘the sky would be the limit’ and extreme claims of any kind could be made”). As

202 Amendments of 1976 when Congress overhauled the post-market surveillance system put in
203 place for devices by the 1938 FD&C Act, replacing it with a comprehensive framework that
204 included premarket review. Among the reasons for the changes to the statute was Congress’
205 concern about unsafe and ineffective marketed devices.¹⁷

206
207 When what exists is preliminary scientific data, the ultimate relevance and utility of that data is
208 often unknown. That is, one might truthfully summarize the data generated by a preliminary
209 study without being able to determine whether any inferences or conclusions drawn from the
210 data would ultimately be shown to be correct.¹⁸ If the government bears the burden to prove that
211 a communication is false or misleading, the government may not be able to meet that burden
212 until after the evidence is generated to establish that the product is unsafe or ineffective (and
213 relief is likely to come too late to prevent harm to members of the public). The requirement for
214 premarket review reflects Congress’ determination that, where there is an absence of
215 scientifically robust evidence, firms should not be free to market a product based merely on
216 conjecture or rosy predictions, even if well-intentioned or logical.¹⁹ Where emerging and
217 developing scientific data are not yet sufficiently complete or robust to determine that a medical
218 product causes the observed benefit and that the risks are outweighed by the benefit, claims of
219 safety and effectiveness are misleading. Premarket review addresses that problem by placing the
220 burden of uncertainty on the firm – by restricting the firm’s distribution of its product for an
221 unapproved use, the requirement obligates the firm to develop robust data that enables a reliable
222 evaluation and determination of safety and effectiveness for new uses.

223
224 b. Protecting Against Fraud, Misrepresentation and Bias through Robust
225 Review by an Independent Scientific Agency. FDA premarket review also assures that safety
226 and efficacy are evaluated on a population level under rigorous scientific standards by
227 independent, scientifically expert reviewers. The history of public health tragedies caused by
228 medical products demonstrates that there have been some unscrupulous players in the
229 marketplace who have made deceptive or unsubstantiated claims about medical products.²⁰ Even

the Secretary of Health, Education, and Welfare told Congress, “[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a firm can fool the public until the [FDA] finally catches up with him” (The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the Comm. on the Judiciary, 87th Cong., 2d Sess. 171 (1962)).

¹⁷ For congressional history regarding the need for the Medical Device Amendments of 1976, see S. REP. NO. 94-33, at 2-6 (1975) and H.R. REP. NO. 94-853, at 5-12 (1976).

¹⁸ See Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 560-61 (2014) (“In this realm, truth or falsity is not knowable a priori. Any knowledge of truth or falsity emerges from our economic and temporal investments”).

¹⁹ See S. REP. NO. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2902 (“On what logical basis can one possible [sic] argue that the initial claim for a drug, say the relief of headaches, should be supported by ‘substantial evidence,’ but that successive claims, for instance the cure of acne, need not be so supported? The considerations which would warrant examination and approval of the initial claim would be just as appropriate and compelling for successive claims.... [Otherwise] extreme claims of any kind could be made, subject only to the very cumbersome power of the FDA to seize a single specific shipment of the drug as misbranded. It takes months or years to go through the legal st[e]ps leading to an injunction-- for contempt of court-- against the company to prevent continuing marketing of interstate commerce. In the past 2 dozen years, FDA has invoked its seizure powers against not more than two or three prescription drugs”).

²⁰ See generally, e.g., Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299 (2003).

230 where a firm is not deliberately manipulating the message, independent scientific review helps
231 ensure that conclusions about the product are adequately supported and unbiased.²¹ As created
232 and assigned by Congress, FDA conducts this review to evaluate whether a medical product is
233 safe and effective for a particular use by comparing the demonstrated therapeutic benefit of that
234 use against the product’s risks. In its premarket reviews, FDA evaluates, among other things,
235 safety and efficacy data gathered and/or generated by the firm to verify that the applicable
236 standards for safety and efficacy have been met. For example, in implementing these
237 requirements for new drug applications (NDAs), FDA requires the submission of, among other
238 things, data and information on chemistry, manufacturing, and controls; nonclinical
239 pharmacology and toxicology; human pharmacokinetics and bioavailability; microbiology;
240 clinical data; and statistical evaluations of clinical data.²² Similar requirements exist for certain
241 devices and new animal drugs.²³ FDA generally evaluates medical devices using clinical (e.g.,
242 adequate, well-controlled investigations, partially controlled studies, studies and objective trials
243 without matched controls) and non-clinical studies (e.g., microbiological, toxicological,
244 immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests)
245 with the device.²⁴ Over the past several years, FDA has also developed an enhanced approach to
246 benefit-risk assessment in regulatory decision-making for human drug and device products that
247 takes into account the patient perspective, including on disease severity and current available
248 options in a therapeutic area, and on the risks and benefits that matter most to them.²⁵ In
249 addition to reviewing the summarized reports of studies submitted as part of an application, FDA
250 can review underlying data and inspect clinical trial records, which allows the Agency to
251 examine the integrity of the data on which its review is based.²⁶

252
253 For each of these and other topics relevant to a particular application, FDA assigns review teams
254 and primary reviewers who specialize in that scientific discipline to review that portion of the
255 application and to generate a written evaluation.²⁷ FDA then integrates the conclusions from

²¹ See, e.g., Joel Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167 (2003) (reviewing 30 studies finding that “[s]ystematic bias favours products which are made by the company funding the research.”); Andreas Lundh et al., *Industry Sponsorship and Research Outcome*, THE COCHRANE COLLABORATION (2013) (reviewing 48 studies showing that “[s]ponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources.”).

²² See 21 C.F.R. § 314.50. See also Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW. ENG. J. MED. 1727, 1730 (2008) (“In the pharmaceutical market, determining whether a drug is safe and effective for an intended use can involve dozens of FDA scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials. In essence, the agency acts as a learned intermediary on behalf of prescribing physicians.”).

²³ See 21 C.F.R. §§ 514.1 and 814.20.

²⁴ See Appendix A for a more complete discussion of the relevant statutory provisions and implementing regulations.

²⁵ See FDA, *Enhancing Benefit Risk-Assessment in Regulatory Decision-Making*, at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm> (last updated July 7, 2015); FDA, *CDRH Patient Engagement*, at <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhpatientengagement/default.htm> (last updated Nov. 4, 2016).

²⁶ See, e.g., 21 C.F.R. §§ 312.58, 312.68, 511.1, and 812.145.

²⁷ See FDA, *Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products* (April 2005), at

256 these separate review activities to determine the appropriate outcome for the application. FDA’s
257 multi-disciplinary scientific review cannot be replicated by individual health care providers.²⁸
258

259 This robust independent review protects the public health in several ways. Review by an
260 independent scientific agency ensures that any product approval/clearance is properly evidence-
261 based and that standards are applied consistently across a class of products intended for treatment
262 or diagnosis of a disease or condition. This process protects the public from uses for which the
263 benefits do not outweigh the risks, either because of the direct adverse effects caused by the
264 medical product or because the use is ineffective, which can harm patients when the choice of an
265 ineffective product causes them to delay or forego appropriate medical treatment, as well as by
266 exposing them to unnecessary risks. Although some of the assurances from independent review
267 for a particular study can be obtained by review by non-governmental entities (such as peer
268 review coordinated by a scientific or medical journal), the standards governing FDA review
269 provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that
270 are not met by the more narrow examination of the peer review process, given the limited data
271 typically available to and reviewed by peer reviewers, the more limited number of peer reviewers
272 (and thus more limited areas of expertise), and the scope of a journal article.²⁹ When review is

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>;
FDA, *The 510(k) Process: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]*, *Guidance for Industry and Food and Drug Administration Staff* (July 2014) at
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>;
FDA, *Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)*, *Guidance for Industry and Food and Drug Administration Staff* (Dec. 2012), at
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm313368.pdf>;
FDA, *Guidance for Industry, Administrative Applications and the Phased Review Process* (May 2015), at
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052532.pdf>.

²⁸ See Aaron S. Kesselheim et al., *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 JAMA 445, 446 (2013) (“It is not ‘paternalistic’ to recognize the obstacles that prevent physicians from [sorting through marketing claims and making sound decisions on their own] when it comes to off-label prescribing. FDA approval involves numerous highly skilled scientists reviewing a great deal of data for months. It is not possible for individual prescribers to conduct the same rigorous evaluation, even if such data are available to them (which they often are not) or to expect that sales representatives’ presentations will effectively meet this need.”); Chester B. Good & Walid F. Gellad, *Off-Label Drug Use and Adverse Events, Turning up the Heat on Off-Label Prescribing*, 176 JAMA INTERN MED. 63-64 (Jan. 2016) (“Even in situations where an off-label indication has been studied, pharmacokinetics, drug-disease interactions, and other safety considerations are unlikely to have been studied systematically to the level required during the FDA drug approval process. Likewise, few clinicians have the time or the motivation to review evidence for those off-label indications to arrive at a balanced assessment of the risks and benefits to support the appropriate use of that drug”); Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295 (Mar. 2016) (“Although physicians are a more sophisticated audience, they are not in a position to substitute for regulators. Relatively few have training in research methods. Those who do have such training lack access to comprehensive clinical trial data and rely heavily on the published literature, which is skewed toward positive results.”); Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427-28 (2008) (“[O]ff-label use . . . undercuts expectations that drug safety and efficacy have been fully evaluated.”). See also Brian S. Alper et al., *How much effort is needed to keep up with the literature relevant for primary care?*, 92 J MED LIBR ASS’N 429-37 (2004) (study on overall workload of systematically keeping up with the medical literature relevant to primary care estimated that it would require 627.5 hours per month).

²⁹ Compare *supra* notes 22-27 and accompanying text with discussion regarding the limitations of the peer review process in Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome*

273 conducted by private entities, the review could also be influenced by industry affiliation or other
274 biases.³⁰ Furthermore, the results of negative trials often are unpublished, which limits
275 stakeholders’ access to data that calls into question a medical product’s safety or effectiveness
276 for a particular use.³¹

277
278 c. Preventing Diversion of Limited Health Care Resources. Promotion
279 regarding unapproved uses of approved/cleared medical products may lead to the diversion of
280 limited health care resources. The expenditure of resources on unsafe or ineffective products is
281 itself wasteful, limits the availability of these resources for safe and effective treatments, and
282 causes financial harm to consumers, private insurers, and government health care programs. In
283 addition, when there are adverse health consequences from the use of unsafe and/or ineffective
284 products, the additional treatment of those consequences increases costs, causing a negative
285 impact on patients (or, for animals, caretakers), private insurers, and government health care
286 programs.³²

287
288 **3. Ensuring Required Labeling is Accurate and Informative**
289

290 Medical product labeling is intended to provide an accurate and informative statement of the
291 scientific data and information necessary for the safe and effective use of the product. FDA
292 plays a pivotal role in helping to ensure that required labeling for a drug or medical device is
293 accurate and informative. For example, the FDA process for reviewing a drug firm’s or certain
294 device firm’s clinical studies leads to approved product labeling that conveys important
295 information related to the safe and effective use of the product for its intended use, such as

Reporting Bias—An Updated Review, 8 PLOS ONE e66844 (2013); Tom Jefferson et al., *Effects of Editorial Peer Review: A Systematic Review*, 287 JAMA 2784-86 (2002); Fiona Godlee et al., *Effect on the Quality of Peer Review of Blinding Reviewers and Asking Them to Sign Their Reports: A Randomized Controlled Trial*, 280 JAMA 237-40 (1998); Mohammadreza Hojat et al., *Impartial Judgment by the “Gatekeepers” of Science: Fallibility and Accountability in the Peer Review Process*, 8 ADVANCES IN HEALTH SCI. EDUC. 75-96 (2003); Marlies van Lent et al., *Role of Editorial and Peer Review Processes in Publication Bias: Analysis of Drug Trials Submitted to Eight Medical Journals*, 9 PLOS ONE e104846 (2014); Sara Schroter et al., *Effects of Training on Quality of Peer Review: Randomized Controlled Trial*, 328 BRIT. MED. J. 673 (2004). Also compare *supra* note 26 and accompanying text (discussing FDA’s ability to review underlying data and inspect clinical trial records) with Charlotte J. Haug, *Peer-Review Fraud — Hacking the Scientific Publication Process*, 373 NEW ENG. J. MED. 2393-95 (2015); Alok Jha, *False positives: fraud and misconduct are threatening scientific research*, THE GUARDIAN (Sept. 13, 2012) (as amended online at <https://www.theguardian.com/science/2012/sep/13/scientific-research-fraud-bad-practice>).

³⁰ See, e.g., *supra* note 21.

³¹ See, e.g., Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016); Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias—An Updated Review*, 8 PLOS ONE e66844 (2013).

³² Roberto Cardarelli et al., *A Cross-Sectional Evidence-Based Review of Pharmaceutical Promotional Marketing Brochures and Their Underlying Studies: Is What They Tell Us Important and True?*, 7 BMC FAM. PRACTICE 1-2 (2006) (pharmaceutical industry marketing to prescribing physician creates the potential for prescribing practices that may not benefit the patient, which contribute to escalating health care costs); Michael A. Steinman & Dean Schillinger, *Drug Detailing in Academic Medical Centers: Regulating for the Right Reasons, with the Right Evidence, at the Right Time*, 10 AM. J. BIOETHICS 21, 22 (2010) (the evidence “strongly suggests that detailing achieves its intended effect of increasing the volume of prescriptions written by physicians for the higher cost, brand-name products marketed by industry.”).

296 indications, dosage, precautions, warnings, and contraindications. Accurate and informative
297 labeling is an essential tool to help ensure appropriate prescribing practices and use of the
298 product; indeed, a product is misbranded if it lacks labeling that adequately informs patients and
299 practitioners how to use the product safely for the uses for which it is intended. When medical
300 products are used for unapproved uses, health care providers and consumers do not have the
301 benefit of any FDA-required labeling related to that use and designed to assure there is adequate
302 information to support safe and effective selection and administration for that use. In the
303 absence of accurate information on how to use a medical product safely and effectively for an
304 unapproved use, including the lack of such important information as appropriate dosing,
305 contraindications, or instructions for use, there is a significant potential for harm to patients.
306

307 **4. Protecting the Integrity and Reliability of Promotional Information Regarding** 308 **Medical Product Uses** 309

310 The FDA Authorities also help protect the integrity and reliability of the promotional
311 information in the medical marketplace, which helps health care providers and consumers make
312 informed decisions. Before these requirements were in effect, medical products were commonly
313 marketed for uses when there was little or no evidence of their effectiveness. For example, after
314 the passage of the Kefauver-Harris Amendments, FDA retained the National Academy of
315 Sciences to evaluate the effectiveness of the 16,500 uses claimed on behalf of the 4,000 drugs
316 marketed under NDAs in 1962. Seventy percent of these claimed uses were found not to be
317 supported by substantial evidence of effectiveness, and only 434 drugs were found effective for
318 all their claimed uses.³³ Prior to the passage of the Kefauver-Harris Amendments, the
319 advertising of these products was subject to the Federal Trade Commission Act, including the
320 restrictions on false advertisements.³⁴ Even so, the vast majority of these drugs were marketed
321 for ineffective and/or dangerous uses.³⁵ In this environment, health care providers and other
322 audiences could not trust or rely on the promotional information in the medical marketplace, as
323 the uses for which the products were marketed were more likely to be ineffective than effective.
324 Such an environment also made it difficult to distinguish any useful products from the shams.³⁶
325
326 More recent studies have similarly found that the majority of unapproved uses for which drugs
327 are prescribed lack adequate evidence of effectiveness,³⁷ and that the risk of adverse events is

³³ See *Weinberger v. Hynson, Westcott and Dunning*, 412 U.S. 609, 621 (1973).

³⁴ See *Wheeler-Lea Act of 1938*, Pub. L. No. 75-447, 52 Stat. 111 (1938), amending the Federal Trade Commission Act, 15 U.S.C. §§ 52-57.

³⁵ See Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299 (2003); see also Kate Greenwood, *The Ban on “Off-Label” Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False and Misleading Commercial Speech?*, 37 AM. J. L. & MED. 278, 291-92 (2011) (describing the history of misleading firm claims in promoting unapproved uses).

³⁶ See S. REP. NO. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2898, 2901.

³⁷ See David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN. MED. 1021-1026 (2006) (Using data from a nationally representative survey of office-based physicians in an attempt to systematically describe the overall magnitude of off-label prescribing in general outpatient care as a function of the strength of scientific support for those practices, the authors found that 21 percent of the 725 million total drug prescriptions in 2001 were for off-label uses and that most of these off-label uses (73 percent) lacked evidence of clinical efficacy); Surrey M. Walton et al., *Prioritizing Future Research on Off-Label Prescribing: Results of a*

328 higher for unapproved versus approved uses, and even higher when the unapproved use is not
329 supported by reliable scientific data.³⁸ Many devices and drugs that appear promising based on
330 early stage research have ultimately failed to show clinical benefit in later phase research, while
331 increasing risk among patients.³⁹ Furthermore, results for the majority of studies of failed uses
332 are not published in peer-reviewed journals.⁴⁰

333

334 Research has also shown that marketing of drugs toward health care providers drives prescribing
335 practices, including prescribing for unapproved uses, and that commonly used marketing
336 techniques can influence prescribing decisions in a manner that is not in the patient’s best
337 interest.⁴¹ Studies have found that health care providers overestimate their knowledge of what

Quantitative Evaluation, 28 PHARMACOTHERAPY 1443-1452 (2008) (In examining the top 25 drugs in terms of total combined off-label uses with inadequate evidence of effectiveness for January 1, 2005 through June 30, 2007, the authors found that 29 percent of all uses for these drugs were off-label and 82 percent of these off-label uses had inadequate evidence of efficacy. If uses that were supported by uncertain evidence of efficacy were also included, 90 percent of all off-label uses had either inadequate or uncertain evidence of efficacy); Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016) (In a study conducted in Quebec, Canada examining prescriptions from 2005 through 2009, 11.8 percent of the prescriptions were for off-label uses and 80.9 percent of these off-label uses lacked strong scientific evidence).

³⁸ Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN MED. 55-63 (Jan. 2016); Tewodros Eguale et al., *Comment & Response: In Reply to In Defense of Off-label Prescribing*, 176 JAMA INTERN MED. 861-62 (June 2016) (“Unscientific prescribing constitutes 4 of 5 off-label uses, and this unscientific prescribing has resulted in a 54% increased risk of adverse drug events compared with on-label uses.”).

³⁹ See, e.g., Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016) (the authors found that more than half of drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of inadequate efficacy, safety, or both).

⁴⁰ See, e.g., Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016); Kerry Dwan et al., *Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias—An Updated Review*, 8 PLOS ONE e66844 (2013).

⁴¹ See, e.g., Puneet Manchanda & Elisabeth Honka, *The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review*, 5 YALE J HEALTH POLICY LAW ETHICS 785-822 (2005) (summarizing a number of studies establishing that detailing has a significant positive impact on physician prescription behavior, even while other studies indicate many physicians do not consider information from sales representatives to be accurate); Ian Larkin et al., *Restrictions on pharmaceutical detailing reduced off-label prescribing of anti-depressants and antipsychotics in children*, 33 HEALTH AFFAIRS 1014-23 (2014) (finding that detailing strongly affected prescribing of antidepressants and antipsychotics in children, including for unapproved uses); Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295 (Mar. 2016) (“To be effective, a company’s marketing must also influence the prescribing patterns of physicians. . . . [T]here is a strong and specific association between pharmaceutical marketing and physician behavior, independent of the evidence supporting the products.”); Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1730 (2008) (“[M]anufacturers could potentially bury physicians and patients in an avalanche of ‘information’ to promote drugs, including reports of individual cases, uncontrolled or biased clinical studies, and poorly conducted observational analyses . . . chosen selectively to create an appearance of safety or efficacy that would not meet FDA standards.”); Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 698 (2014) (“The information that sales representatives provide is more likely to be biased than truthful. They are trained to emphasize the benefits of their product, to suppress any negative information about their product, and to highlight negative aspects of a competitor’s product. Thus, although manufacturers are in a unique position to

338 uses are FDA-approved for drugs and assume that many unapproved uses are supported by sound
339 scientific evidence when they are supported by uncertain or no evidence.⁴² Marketing activities
340 and communications regarding the safety and effectiveness of a medical product for a particular
341 use that are not properly supported by scientific evidence may thus create a false or misleading
342 impression about the safety and efficacy of the medical product for that use, which can lead to
343 prescribing or use decisions that harm patients.⁴³ Examples of some marketing activities that
344 caused such harm are described in Appendix C.
345
346 The requirements of the FDA Authorities, including the evidence generation requirements and
347 the prohibitions on distributing products for unapproved uses, help protect the integrity and

provide information to the medical community, they are more likely to control the information in a manner that best advances sales”); Kate Greenwood, *The Ban on “Off-Label” Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False and Misleading Commercial Speech?*, 37 AM. J.L. & MED. 278, 292 (2011) (discussing evidence of misleading marketing by pharmaceutical sales representatives); Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. Rev. 1539, 1581-82 (2014) (citing published reports of pharmaceutical sales representatives admitting to spinning information to convey the positive while downplaying the negative).

⁴² See Donna T. Chen et al., *U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey*, 18 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 1094-1100 (2009) (study examining physicians’ knowledge of the FDA-label status of commonly used prescription drugs found that a significant percentage prescribed some drugs for unapproved uses in the belief that the uses were approved when there was uncertain or no evidence supporting that use).

⁴³ See, e.g., Jerry Avorn et al., *Forbidden and Permitted Statements about Medications – Loosening the Rules*, 373 NEW ENG. J. MED. 967, 971-72 (2015) (“Considerable research shows that marketing can drive prescribing practices, which in turn can lead to adverse patient outcomes if those decisions are not evidence-based.”); Micah L. Berman, *Manipulative Marketing and the First Amendment*, 103 GEORGETOWN L.J., 497, 518, 522 (2015) (“Marketing, neuromarketing, and social psychological research have all converged on ‘dual-processing models’ of human thought and behavior, which posit that ‘behavior is produced by both intentional, conscious, ‘explicit’ thought and unintentional, nonconscious, ‘implicit’ thought.’ [citation omitted] . . . [M]arketing and psychological research . . . suggests that marketers (1) are most successful when emotional content—not information—is presented to consumers, (2) can carefully craft marketing appeals (using humor and other noninformational techniques) to increase the viewer’s/reader’s receptivity to the marketing message while disengaging critical faculties, and (3) can influence consumer behavior without consumers being aware of the powerful effect of advertising.”); Kristen E. Austad et al., *Association of Marketing Interactions With Medical Trainees’ Knowledge About Evidence-Based Prescribing: Results From a National Survey*, 174 JAMA INTERN MED. 1283, 1288-89 (2014) (“[O]ur data add to the literature showing that pharmaceutical marketing is associated with less-evidence-based prescribing choices and greater inclination to prescribe brand-name products over less expensive generic options or nondrug treatment plans that have equal or greater comparative effectiveness. . . . [T]rainees with fewer connections to industry promotional activities had greater knowledge of evidence-based prescribing Our study is another reminder of the negative effects those interactions can have on the quality and cost of patient care.”); Jerry Avorn et al., *Scientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 AM. J. OF MED. 4, 7-8 (1982) (“Although the vast majority of practitioners perceived themselves as paying little attention to drug advertisements and detail men, as compared with papers in the scientific literature, the [data] revealed quite the opposite pattern of influence in large segments of the sample. . . . [T]he predominance of nonscientific rather than scientific sources of drug information is consistent with what would be predicted from communications theory and marketing research data. Drug advertisements are simply more visually arresting and conceptually accessible than are papers in the medical literature, and physicians appear to respond to this difference.”); see also generally Shelly Chaiken et al., *Heuristic and Systematic Information Processing within and beyond the Persuasion Context*, in UNINTENDED THOUGHT 212 (James E. Uleman ed., 1989); Richard E. Petty & John T. Cacioppo, *The Elaboration Likelihood Model of Persuasion*, in ADVANCES IN EXPERIMENTAL SOCIAL PSYCHOLOGY 123 (Academic Press, Inc. 1986).

348 reliability of the promotional information in the medical marketplace by helping to ensure that
349 the uses for which medical products are marketed are ones for which they have been shown to be
350 safe and effective, and that these products have labeling that provides appropriate directions for
351 these uses. In this way, the FDA Authorities serve to promote the flow of truthful, non-
352 misleading, and scientifically valid promotional information.

353

354 **5. *Protecting Human Subjects Receiving Experimental Treatments, Ensuring***
355 ***Informed Consent, and Maintaining Incentives for Clinical Trial Participation***

356

357 The protection of human subjects receiving experimental treatments is an important public health
358 goal, and Congress has required FDA to issue regulations governing the investigational use of
359 medical products in clinical trials. As Congress directed, these regulations generally require
360 investigators to obtain informed consent before studying a medical product for an unapproved
361 use in human subjects.⁴⁴ The regulations also prescribe other requirements for the conduct of
362 clinical trials. These requirements are designed to provide protections to human subjects when
363 products are studied for unapproved uses. The same protections are not routinely provided when
364 approved/cleared medical products are prescribed to patients for unapproved uses as part of their
365 medical care. Several presenters at the November 9-10, 2016 public hearing who experienced
366 adverse events associated with the unapproved use of approved or cleared medical products
367 noted that they did not know, prior to using the product, that the use for which they were
368 prescribed the product was unapproved. They further indicated that it would have impacted their
369 decision to use the product if they had been told that the use for which it was being prescribed
370 for them was not approved by FDA, and advocated providing this information to patients before
371 a product is prescribed or administered for an unapproved use.

372

373 With regard to maintaining incentives for clinical trial participation, firms' actions to promote
374 widespread use of approved/cleared medical products for unapproved uses may undermine the
375 clinical trial process, and thus ultimately impede the development of robust and reliable scientific
376 data to better support medical decision-making. Particularly if there is the prospect that they
377 may be assigned to a placebo arm, potential participants who believe they may benefit from the
378 use of a product that has not been approved/cleared to treat their condition may decide not to join
379 a clinical trial designed to rigorously examine safety and effectiveness of the medical product for
380 that investigational use. If enough potential participants make the same decision, the study may
381 not have sufficient statistical power to determine whether any observed effect is truly due to the
382 product and not to chance, or may not be able to go forward at all. Accordingly, sponsors would
383 have more difficulty developing data of an adequate quality and quantity to permit review and
384 approval of the safety and effectiveness of the medical product.⁴⁵

⁴⁴ See 21 U.S.C. §§ 355(i)(4) and 360j(g)(3)(D); 42 U.S.C. § 262(a)(2)(A); 21 C.F.R. Part 50. There are narrow exceptions to the informed consent requirements. See 21 U.S.C. §§ 355(i)(4) and 360j(g)(3)(D); see also 21 C.F.R. § 50.23 (providing exceptions to informed consent requirements in several specified situations and upon waiver by the President of the United States to a member of the armed forces); 21 C.F.R. § 50.24 (providing for exception from informed consent requirements for “emergency research”).

⁴⁵ For example, with respect to human drugs, FDA has long recognized that expanded access to unapproved products has the potential to interfere with enrollment in clinical trials. In the 1987 treatment Investigational New Drug (IND) regulations, FDA authorized a treatment IND only if “[t]he drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed” (21 C.F.R.

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6. *Protecting Innovation Incentives, Including Statutory Grants of Exclusivity*

The FDA Authorities provide robust incentives for innovation by ensuring that drug firms have meaningful patent protection and a period of marketing exclusivity (i.e., exclusive marketing rights granted by FDA upon approval of a drug) for certain innovations and for changes to approved drugs.⁴⁶ The relevant legislation, such as the Drug Price Competition and Patent Term Restoration Act (commonly known as the Hatch-Waxman Amendments), was carefully crafted by Congress to seek to ensure that, on the one hand, brand-name pharmaceutical manufacturers whose changes to their drug products meet certain criteria would have meaningful patent protection and a period of marketing exclusivity to enable them to recover their investments in the development of new products and new uses for previously approved products, spurring innovation in pharmaceutical research and development; while, on the other hand, ensuring that once applicable patent protection and exclusivity for these new drugs has expired, consumers would benefit from the rapid availability of lower-priced generic versions of innovator products.⁴⁷ During the time that relevant patent protection or exclusivity is in effect for a new condition of use, FDA may not approve other applications for the protected use. For example, if a drug is approved for one use and is later granted a period of three-year Hatch-Waxman exclusivity for a new use, FDA may not approve a generic version of that drug for that change before the expiration of the three-year exclusivity.⁴⁸ The generic drug can only be approved and labeled for non-protected conditions of use during the three-year exclusivity term,⁴⁹ and it cannot

§ 312.34(b)(1)(iii); 52 Fed. Reg. 19466, 19476 (May 22, 1987)). Subsequent regulations for investigational device exemptions (IDEs) similarly state that FDA will only consider a treatment IDE if, among other things, “[t]he device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed” (21 C.F.R. § 812.36(b)(3); 62 Fed. Reg. 48940, 48947 (Sept. 18, 1997)). Both FDA and firms have recognized this important concern. The current regulations on expanded access for drugs also address these issues. *See* 21 C.F.R. § 312.305(a)(3).

⁴⁶ *See* 21 U.S.C. §§ 355(j)(5)(B) and (F); 21 C.F.R. § 314.108 (new drug product exclusivity); *see also* 21 U.S.C. § 360cc and 21 C.F.R. § 316.31 (orphan drug exclusivity); 21 U.S.C. § 355a (pediatric exclusivity); 21 U.S.C. § 360b(c)(2)(F). The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) (subtitle A of Title VII of Pub. L. 111-148, 124 Stat 119 (2010)) also provides for exclusivity periods for biological products licensed under section 351(a) of the Public Health Service Act (PHS Act) (see, e.g., sections 351(k)(7) & (m) of the PHS Act (42 U.S.C. §§ 262(k)(7) & (m)); section 7002(h) of the BPCI Act).

⁴⁷ H.R. REP. NO. 98-857, pt. 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-2648. The goal of the BPCI Act is similar, in concept, to that of the Hatch-Waxman Amendments.

⁴⁸ 21 U.S.C. § 355(j)(5)(F)(iv).

⁴⁹ Three-year exclusivity does not prevent the submission or approval of every application that references the product with the exclusivity protection. Instead, it protects against the approval of a 505(b)(2) application or abbreviated new drug application (ANDA) for the conditions of approval of the original new drug application, or for a change approved in the supplemental new drug application. 21 U.S.C. § 355(j)(5)(F)(iii) and (iv). A generic drug can be approved for less than all of the indications for which the brand drug has been approved; generic applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use. *See* H.R. REP. NO. 98-857, pt.1, at 21 (“The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.”); 21 C.F.R. § 314.92(a)(1) (a proposed generic drug product must have the same conditions of use as the listed drug, except that “conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted”). The regulations at 21 C.F.R. § 314.127(a)(7) further provide that to approve a generic drug application containing proposed labeling that omits “aspects of the listed drug’s labeling [because those aspects] are protected by patent, or

406 be marketed for the protected conditions of use during the exclusivity term. If firms promote
407 their approved drugs for unapproved uses, including for conditions of use that are protected by
408 patents or exclusivity held by another applicant, it would undermine these incentives for
409 innovation in the FDA Authorities.⁵⁰

410

411 **7. *Promoting the Development of Products for Underserved Patients***

412

413 The FDA Authorities provide a number of incentives and alternative review pathways aimed at
414 encouraging development of safe and effective medical products for underserved patient
415 populations. For example, there are a number of FDA programs that are intended to facilitate
416 and expedite development and review of new medical products to address unmet medical needs
417 in the treatment of a serious or life-threatening conditions, including fast track drug designation,
418 breakthrough therapy/device designation, accelerated drug approval, expedited access program
419 for certain devices, and priority review drug designation. These programs help ensure that
420 therapies for serious conditions are approved/cleared and available to patients as soon as it can
421 be concluded that the therapies' benefits justify their risks.⁵¹ The FDA Office of Orphan
422 Products Development (OOPD) also works to advance the evaluation and development of
423 products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis
424 and/or treatment of rare diseases or conditions. OOPD implements programs that provide
425 incentives and an alternative review pathway for sponsors to develop products for rare diseases,
426 including through the Orphan Drug Designation program (which can result in a period of seven
427 year orphan-drug exclusivity upon approval), the Rare Pediatric Disease Priority Review
428 Voucher program, the Humanitarian Use Device program, and three extramural grant
429 programs.⁵² Through these programs, OOPD has successfully enabled the development and
430 marketing of more than 575 drugs and biological products for rare diseases since 1983 and more
431 than 65 Humanitarian Device Exemption approvals.⁵³ These incentives and programs recognize
432 the importance of the public health protections advanced by the FDA premarket review
433 framework for underserved patient populations, and are intended to facilitate the development of
434 approved or cleared therapies for such populations. If firms promote their approved or cleared
435 medical products for unapproved uses, these incentives and programs could be weakened.

436

by exclusivity,” FDA must find that the “differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.”

⁵⁰ See *Spectrum Pharms., Inc. v. Burwell*, 824 F.3d 1062, 1068 (D.C. Cir. 2016) (recognizing the need for FDA misbranding enforcement action to deter manufacturer promotion of a generic drug for use approved for the sponsor but not for the generic).

⁵¹ See FDA, *Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>.

⁵² See FDA, *Developing Products for Rare Diseases & Conditions*, at <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm> (last updated Jan. 5, 2017).

⁵³ *Id.*

437 **B. How Firm Communications Regarding Unapproved Uses of Approved or**
438 **Cleared Medical Products Can Advance Public or Individual Health Interests**
439

440 **1. *Supporting Informed Decision-Making for Patient Treatment***
441

442 In its premarket reviews, FDA evaluates, among other things, safety and efficacy data gathered
443 and/or generated by the firm to verify whether there are adequate tests to show safety and
444 substantial evidence of efficacy (for drugs) or a reasonable assurance of safety and effectiveness
445 (for devices). FDA evaluates this information and makes an approval/clearance decision based
446 on a determination of the safe and effective use of the product in the general population(s)
447 included in the studies submitted in the application.
448

449 However, after the initial approval/clearance, questions arise in practice relating to the use of
450 products for particular patients. Health care providers prescribe and use medical products for
451 unapproved uses when they judge that the unapproved use is medically appropriate for their
452 particular patients – whose characteristics and needs may differ from the characteristics of the
453 population studied for the approved/cleared uses. This practice may be most common in patients
454 with diseases for which there is no proven treatment, or in patients who have exhausted all
455 approved/cleared treatments.⁵⁴
456

457 As discussed in the preceding section, Congress and FDA have taken steps to incentivize and
458 expedite the successful development of more and better treatments that will be safe and effective
459 for underserved patient populations. Notwithstanding these efforts, several presenters at the
460 November 9-10, 2016 public hearing maintained that there is still a need for information about
461 unapproved uses of approved or cleared products for these special populations. Thus, while the
462 FDA Authorities have incentivized the successful development of many important treatments for
463 underserved patient populations, the reality remains at any point in time that for some patients,
464 approved/cleared therapies are not available or have failed. In such instances, both health care
465 providers and patients may be interested in information about unapproved uses of products, and
466 payers and similar entities have also expressed interest in information that is potentially relevant
467 to coverage decisions which affect patient care.
468

469 **2. *Furthering Scientific Understanding and Research***
470

471 In addition, reliable scientific information regarding unapproved uses may help further scientific
472 research, such as through hypothesis generation, and increasing scientific understanding in new

⁵⁴ See 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, 304 (2010) (“[T]here is little doubt that in oncology and pediatrics off-label prescribing is exceedingly common. . . . [I]n some therapeutic areas off-label uses are the customary, preferred treatments.”); Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (“Physicians’ freedom to prescribe drugs off-label carries important advantages. It permits innovation in clinical practice, particularly when approved treatments have failed. . . . And it can provide the only available treatments for ‘orphan’ conditions.”); Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1730 (2008) (“In certain patient groups, such as children and patients with rare diseases, off-label use may reflect the standard of care.”).

473 and developing areas.⁵⁵ Making the data and information public may also encourage the
474 collection of outcomes through surveillance and reporting, stimulate appropriate additional
475 evidence generation, and identify unapproved uses that are likely to present an unreasonable risk
476 to patients. Sharing information may also allow for collaborative efforts to develop new
477 treatments or improve existing ones.
478

479 In September 2016, the Department of Health and Human Services (HHS) issued a final rule⁵⁶
480 that clarifies and expands requirements for the submission of certain objective results
481 information from clinical trials to a publicly available website – ClinicalTrials.gov – pursuant to
482 section 402(j) of the Public Health Service Act.⁵⁷ Neither the statute nor the rule authorize any
483 promotion of unapproved uses of approved or cleared medical products. The rule recognizes
484 several research-related benefits from the disclosure of this objective results data including:
485 facilitating assessments of the quality and appropriateness of trial reporting; aiding in the
486 identification of knowledge gaps for trials of all types of products; helping investigators avoid
487 repeating trials on medical products that have been found to be unsafe or unsuccessful; helping
488 determine where information might be missing from the literature (e.g., missing trials, missing
489 outcome measures); and honoring the contribution of the clinical trial volunteers by creating a
490 public record of the trial and its results.
491

492 * * *

493
494 FDA believes there is widespread agreement that no government interests are served by firm
495 communications that do not fairly present reliable scientific information. A firm communication
496 that conveys scientific information that is not truthful, complete, or balanced or that lacks
497 scientific validity has at least the potential to mislead the audience and does not contribute
498 meaningfully to the marketplace of ideas.⁵⁸ Similarly, firm communications that are designed to

⁵⁵ See Jeffrey K. Francer & Natalie A. Turner, *Responsible Clinical Trial Data Sharing: Medical Advancement, Patient Privacy, and Incentives to Invest in Research*, 8 J. HEALTH & LIFE SCI. L. 63 (2014) (“Responsible data sharing agreements between biopharmaceutical companies and qualified researchers for clinical trial data and information at different stages of the drug development process may help improve public health, increase innovative drug development, and enhance patient safety through data pooling and analysis.”); Joseph S. Ross & Harlan M. Krumholz, *Ushering in a New Era of Open Science Through Data Sharing*, 309 JAMA 1355 (2013) (“Sharing maximizes the value of collected data and promotes follow-up studies of secondary research questions using existing data.”); Michelle M. Mello et al., *Preparing for Responsible Sharing of Clinical Trial Data*, 369 NEW ENG. J. MED. 1651 (2013) (“Independent researchers may use aggregated participant-level data to explore questions of public health significance that have not been addressed in individual trials. Pooling of these data may increase the precision of estimates of treatment efficacy, detect safety problems unobservable in smaller samples, allow exploration of subgroup effects, and permit analysis of how therapeutic effects vary in different geographic settings because of such factors as population genetics and health care delivery systems.”); 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, 332-33 (2010) (publication of study results “serves to advance the science and . . . enable the medical community to better understand the safety and efficacy profile of the drug”).

⁵⁶ Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64982 (Sept. 21, 2016) (to be codified at 42 C.F.R. pt. 11).

⁵⁷ 42 U.S.C. § 282(j).

⁵⁸ See, e.g., Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century – Off-label Marketing and First Amendment Concerns*, 314 JAMA 1795-96 (2015) (“[T]he marketplace of ideas and physician discretion does not work well without accurate information from well-designed studies.”); Spencer Phillips Hey &

499 cause the audience to reach safety or efficacy conclusions independent of or not supported by the
500 available data are misleading, have the potential to harm patients, and lead to a waste of health
501 care resources.⁵⁹

502
503 Furthermore, the ability to adequately assess benefit and risk for an unapproved use is
504 dramatically impacted by the objective and transparent presentation of data and information.
505 Transparency with respect to the data and information can help ensure scientific validity by
506 promoting scrutiny, evaluation, and public discussion of the data and information by health care
507 entities and other interested and informed stakeholders.⁶⁰ FDA recognizes that technological and
508 business changes are increasingly affecting medical decision-making and prescribing. There are
509 an increasing number of entities in the health care system with a stake in evaluating evidence to
510 assess the rational and systematic use of medical products. For example, many physicians who
511 prescribe medicines or use devices for patient care are employed by large group practices or
512 integrated health systems. Consolidation of practices and hospitals into integrated systems has
513 increased the use of system measurements of quality, with an emphasis on measurement of
514 appropriate use of medical products, including increasing use of analytics to determine access to
515 carefully monitored formularies. Insurance carriers, health care systems, and similar entities also
516 monitor use of medical products, restrict access based on assessments of value, and employ
517 performance measures to monitor appropriate use and outcomes. Transparency through open
518 access to the supportive data underlying firms' communications with these groups and with other

Aaron S. Kesselheim, *An Uninformative Truth: The Logic of Amarin's Off-Label Promotion*, 13 PLOS MED. e1001978 (2016) (“[T]ruthfulness’ is not a sufficiently restrictive criterion for regulating promotional speech as concerns off-label medications. A better and clearer standard would demand that promotional claims must be informative, in the sense that they actually have empirical truth content, which is the assurance that FDA review and validation provides.”); Joanna K. Sax, *Protecting Scientific Integrity: The Commercial Speech Doctrine Applied to Industry Publications*, 37 AM. J.L. & MED. 203, 204, 221 (2011) (stating that tactics by firms to flood the literature with positive information about their products while suppressing negative information may mislead health care providers into using harmful or inferior products); Jerry Avorn et al., *Forbidden and Permitted Statements about Medications — Loosening the Rules*, 373 NEW ENG. J. MED. 967 (2015) (“[F]or both claims of efficacy and statements about side effects, the results of individual studies can be incomplete or misleading while not being outright fraudulent; publication in a peer-reviewed journal does not in itself protect against this. Poorly designed or conducted clinical trials or observational studies can readily overstate benefits or minimize risks; unorthodox or inept statistical analyses can create the impression of efficacy or of safety even when more rigorous assessments would come to a different conclusion.”).

⁵⁹ See, e.g., *supra* notes 41-43.

⁶⁰ See Joseph S. Ross & Harlan M. Krumholz, *Ushering in a New Era of Open Science Through Data Sharing*, 309 JAMA 1355-56 (2013) (“If science is to be progressive and self-correcting, then data, not just summary conclusions, must be open to independent scrutiny. . . . There have been too many prominent examples in which independent analyses of trial data, often made available through litigation but sometimes through public release by the National Institutes of Health, revealed important insights about medical products’ relative balances of benefit and harm that were neither identified nor reported by those who generated the data. Examples include well-known medications such as digoxin, rofecoxib, rosiglitazone, and oseltamivir.”); Jeffrey K. Francer & Natalie A. Turner, *Responsible Clinical Trial Data Sharing: Medical Advancement, Patient Privacy, and Incentives to Invest in Research*, 8 J. HEALTH & LIFE SCI. L. 63 (2014) (“Enhanced clinical trial data sharing may improve the integrity of clinical trials by exposing inappropriate analytical methods and selective use of data, encouraging an accurate portrayal of a drug’s risk-benefit profile, and protecting against publication bias and inaccurate reporting.”); Michelle M. Mello et al., *Preparing for Responsible Sharing of Clinical Trial Data*, 369 NEW ENG. J. MED. 1651 (2013) (“[C]oncern about the completeness, timeliness, and accuracy of sponsor-reported summary results” have led independent researchers to demand access to the underlying data.).

519 interested and informed stakeholders is critical in attempting to safeguard the integrity of the
520 information in the communications.

521
522 **IV. ENSURING A POLICY APPROACH THAT INTEGRATES THE MULTIPLE**
523 **PUBLIC HEALTH INTERESTS TO MAXIMIZE PUBLIC GOOD AND**
524 **REFLECTS APPROPRIATE CONSIDERATION OF THE FIRST AMENDMENT**
525

526 As shown above, there can be, in certain instances, a tension between the public health interests
527 directly advanced by the premarket review requirements and other aspects of the FDA
528 Authorities and other important interests—particularly with regard to patient treatment decisions.
529 As important and successful as the FDA Authorities have been, and continue to be, in
530 incentivizing the successful development of more and better treatments that are safe and
531 effective for more patients with different diseases, the reality remains at any point in time that for
532 some patients, approved/cleared therapies are not available or have failed. While the goal of
533 promoting robust research and development of new products to meet these underserved patients
534 remains important to the public health, the latitude for health care providers to prescribe or use
535 approved/cleared medical products for unapproved uses for their patients functions as a critical
536 safety valve. Cognizant of this, FDA, in implementing the FDA Authorities, has sought to strike
537 a careful balance, supporting medical decision-making for patients in the absence of better
538 options, but doing so without undermining the measures designed to incentivize the development
539 and approval/clearance of medical products that would reduce the need to rely on unapproved
540 use, in light of its risks.

541
542 FDA’s current implementation approach does not proscribe all firm communications about
543 unapproved uses of approved or cleared medical products. FDA has issued guidance documents
544 to describe some of the circumstances when it would not consider a manufacturer’s distribution
545 of reprints, clinical practice guidelines, or reference texts regarding unapproved uses of
546 approved/cleared medical products to be evidence of intended use and/or false or misleading.⁶¹
547 FDA has also issued a draft guidance on responding to unsolicited requests, which states that
548 “FDA has long taken the position that firms can respond to unsolicited requests for information
549 about FDA-regulated medical products by providing truthful, balanced, non-misleading, and
550 non-promotional scientific or medical information that is responsive to the specific request, even
551 if responding to the request requires a firm to provide information on unapproved or uncleared
552 indications or conditions of use.”⁶² FDA has also described how industry may support scientific
553 or educational activities (such as Continuing Medical Education programs) without being subject

⁶¹ FDA, *Revised Draft Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014), at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf>; FDA, *Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, Guidance for Industry* (Jan. 2009), at <http://www.fda.gov/oc/op/goodreprint.html>.

⁶² FDA, *Draft Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011), at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>.

554 to FDA regulation.⁶³ In addition, it has long been FDA policy not to consider a firm’s
555 presentation of truthful and non-misleading scientific information about unapproved uses at
556 medical or scientific conferences to be evidence of intended use when the presentation is made in
557 non-promotional settings and not accompanied by promotional materials. In a similar vein, HHS
558 recently promulgated a rule that clarifies and expands requirements for the submission of certain
559 objective results information from clinical trials to a publicly available website:
560 ClinicalTrials.gov.⁶⁴ Most recently, in January 2017 FDA issued two additional draft guidance
561 documents. One draft guidance addresses firms’ communications of data and information not
562 contained in their products’ approved or required labeling but that are consistent with the FDA-
563 approved or -required labeling and clarifies that such communications alone are not considered
564 evidence of a new intended use.⁶⁵ The other draft guidance addresses firms’ communications
565 with payors and similar entities and provides recommendations on firms’ communications to
566 payors of health care economic information that relates to a drug’s approved indication, as well
567 as recommendations regarding firms’ communications to payors about investigational drugs and
568 devices not yet approved/cleared for any use.⁶⁶

569
570 At our November 9-10, 2016, public meeting, a number of speakers addressed First Amendment
571 considerations. Some asserted that FDA’s current implementation approach appropriately
572 addresses the applicable First Amendment issues. Others asserted that, after *United States v.*
573 *Caronia*,⁶⁷ when an approved or cleared medical product is marketed for an unapproved use,
574 FDA is constrained to regulating such communication only if it is false or misleading. To further
575 this discussion, this section describes the different ways that courts and commentators have
576 addressed the intersection of the FDA Authorities and the First Amendment. To the extent that
577 commenters propose alternatives to FDA’s current approach (whether discussed below or not),
578 we hope that this discussion will inform your comments; it would be very helpful if you would
579 also provide an analysis of how any proposed alternatives would advance the public health
580 objectives the FDA Authorities are designed to promote as compared to FDA’s current
581 implementation approach and other potential alternative approaches discussed in this section.

582 583 **A. Evidence of “Intended Use”**

584
585 Courts have held that the government’s reliance on speech as evidence of intended use under the
586 FD&C Act does not infringe the right of free speech under the First Amendment⁶⁸ based on

⁶³ FDA, *Guidance for Industry, Industry-Supported Scientific and Educational Activities* (Dec. 1997), at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125602.pdf>.

⁶⁴ Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64982 (Sept. 21, 2016) (to be codified at 42 C.F.R. pt. 11).

⁶⁵ FDA, *Draft Guidance for Industry, Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers*, (Jan. 2017), at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶⁶ FDA, *Draft Guidance for Industry, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers*, (Jan. 2017), at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶⁷ 703 F.3d 149 (2d Cir. 2012).

⁶⁸ See *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004); *United States v. Cole*, 84 F. Supp. 3d 1159, 1166 (D. Or. 2015) (The FD&C Act “does not prohibit disease claims as such; it prohibits the sale of products with a particular intent, and disease claims are merely probative evidence of that intent. See 21 U.S.C. § 321(g)(1)(B); 21

587 Supreme Court precedent establishing that “[t]he First Amendment . . . does not prohibit the
588 evidentiary use of speech to establish the elements of a crime or to prove motive or intent.”⁶⁹
589 The D.C. Circuit applied that precedent in the context of the FD&C Act and held that “th[e] use
590 of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is
591 constitutionally valid” and hence “it is constitutionally permissible for the FDA to use speech [by
592 the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer’s]
593 proposed sale . . . would constitute the forbidden sale of an unapproved drug.”⁷⁰
594

595 Under these rulings, the FDA Authorities do not directly prohibit or restrict speech by a firm
596 about unapproved new uses of the firm’s medical products. Instead, the FDA Authorities
597 regulate the introduction of unapproved, adulterated, or misbranded medical products into
598 interstate commerce and the speech of firms may be relevant to establishing an element of a
599 violation of those provisions. Courts have found that FDA can rely on a broad range of
600 evidence, including a firm’s speech, to establish intended use as a medical product and as an
601 element of a prohibited act under the FD&C Act.⁷¹ Although the district court in *Amarin*
602 *Pharma, Inc. v. FDA* held that the *Caronia* decision foreclosed reliance (in the Second Circuit)
603 on the use of speech as evidence of intended use in the context of an FDA enforcement action
604 where the misbranding was based solely on truthful, non-misleading speech regarding the
605 unapproved use of an approved drug,⁷² the Second Circuit later confirmed that “*Caronia* left
606 open the government’s ability to prove misbranding on a theory that promotional speech
607 provides evidence that a drug is intended for a use that is not included on the drug’s FDA-
608 approved label.”⁷³
609

C.F.R. § 201.128. The First Amendment ‘does not prohibit the evidentiary use of speech . . . to prove motive or intent.’ *Wisconsin v. Mitchell*, 508 U.S. 476, 489 . . . (1993). When Defendants incorporate a customer testimonial into advertising material, they endorse and adopt the disease claims made in the testimonial; therefore, the testimonial is evidence of their intent that the product be used to treat disease.”); *United States v. Regenerative Sciences, LLC*, 878 F. Supp. 2d 248 (D.D.C. 2012) (finding product is a drug under FD&C Act based on statements on company website), *aff’d*, 741 F.3d 1314 (D.C. Cir. 2014); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1268 (S.D. Fla. 2005) (allegation that defendant promoted product as a cheap alternative to Botox in workshops, booths, and emails was constitutionally permissible as the indictment sought to punish the defendant “not for his speech, but for the underlying crime evidenced by that speech”); *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 578 (D.N.J. 2004) (“[F]ollowing *Whitaker*, the Government’s restriction of certain labeling, as well as the dissemination of third-party literature, does not violate free speech principles.”); *see also* *United States v. Article of Drug Designated B-Complex Cholinols Capsules*, 362 F.2d 923, 927 (3d Cir. 1966) (statements made by a lecturer employed by a party may be considered evidence of intended use without violating the First Amendment); *United States v. General Nutrition, Inc.*, 638 F. Supp. 556, 562 (W.D.N.Y. 1986) (“[I]t is not speech per se which invokes prosecution.” Instead, the government “contends that in certain circumstances such commentary may become part of the labeling of the product and serve, in a sense, as evidence of a violation of the Act,” and that is constitutionally permissible).

⁶⁹ *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993).

⁷⁰ *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004).

⁷¹ *See, e.g.*, *United States v. Storage Spaces Designated Nos. 8 & 49*, 777 F.2d 1363, 1366 (9th Cir. 1985); *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980); *Nat’l Nutritional Foods Ass’n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). FDA’s regulations reflect this line of cases. *See* 21 C.F.R. §§ 201.128 and 801.4.

⁷² 119 F. Supp. 3d 196 (S.D.N.Y. Aug. 7, 2015).

⁷³ *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613 n.2 (2d Cir. 2016).

610 B. Commercial Speech under *Central Hudson*

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Under the *Central Hudson* framework, the government may prohibit commercial speech that is false, inherently misleading, or actually misleading, and commercial speech related to illegal activity.⁷⁴ If the commercial speech is truthful or potentially misleading, the government may nonetheless impose restrictions on that speech if the restrictions advance a “substantial” government interest and are no “more extensive than is necessary to serve that interest.”⁷⁵

Communications that are not supported by objective and scientifically valid evidence are misleading, have the potential to harm patients, and lead to a waste of health care resources. *Central Hudson* permits the prohibition of such false or inherently misleading communications outright. However, even with respect to communications that are not false or inherently misleading, under the test set forth in *Central Hudson*, restrictions on speech are permitted if they advance substantial government interests in ways that are not more extensive than is necessary to serve those interests. The government’s multi-faceted interests in the public health are substantial and, as described in more detail above, the relevant FDA Authorities directly advance many of those interests.⁷⁶ Nevertheless, as discussed, some of the interests are in tension with each other. Accordingly, analyses of how particular approaches advance the public health interests in this space must address the complex interactions among various interests.

There are several points worth noting regarding the *Central Hudson* evaluation conducted by the Second Circuit panel majority in *United States v. Caronia*. First, the panel majority limited its analysis to addressing the constitutionality of a specific “construction of the FDCA’s misbranding provisions to prohibit and criminalize off-label promotion” (see 703 F.3d 149, 161-64, 166-69 (2d Cir. 2012)), rather than evaluating FDA’s implementation approach. Second, the panel majority did not consider multiple components of public health interests advanced by the FDA Authorities and FDA’s implementation approach.⁷⁷ Finally, the results of the Canadian

⁷⁴ See *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557 (1980); *In re R.M.J.*, 455 U.S. 191, 203 (1982).

⁷⁵ *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980); *1-800-411-Pain Referral Serv., LLC v. Otto*, 744 F.3d 1045, 1055-56 (8th Cir. 2014) (pursuant to *Sorrell v. IMS Health Inc.*, 564 U.S. 552 (2011), courts should assess the constitutionality of commercial speech restrictions under *Central Hudson*). This standard does not require the government to employ “the least restrictive means” of regulation or to achieve a perfect fit between means and ends. *Bd. of Trustees v. Fox*, 492 U.S. 469, 480 (1989). Instead, it is sufficient that the government achieve a “reasonable” fit by adopting regulations “in proportion to the interest served.” *Id.* (quoting *In re R.M.J.*, 455 U.S. at 203). The requirement of narrow tailoring is satisfied “so long as the . . . regulation promotes a substantial government interest that would be achieved less effectively absent the regulation.” *United States v. Albertini*, 472 U.S. 675, 689 (1985).

⁷⁶ See Amy Kapczynski, *Free Speech and Pharmaceutical Regulation—Fishy Business*, 176 JAMA INTERN. MED. 295, 296 (Mar. 2016) (“Commercial speech serves an ‘informational function’ and can be regulated to ensure that the public has access to accurate information. The FDA serves exactly this end. The agency aims not to censor company speech, but to foster the development of accurate and reliable information, and channel that information into settings where it can be rigorously evaluated.”).

⁷⁷ These components include motivating the development of reliable scientific evidence that enables the evaluation of the safety and effectiveness of each intended use of a medical product; requiring that the evidence be developed and independently reviewed before the products are marketed to the general public for each intended use to prevent harm, protect against fraud, misrepresentation and bias, and prevent the diversion of health care resources toward ineffective treatments; and requiring that labeling accompany the product that identifies each approved or cleared

637 study showing an association between unapproved uses and adverse drug events, reported in
638 Tewodros Eguale et al., Association of Off-Label Drug Use and Adverse Drug Events in an
639 Adult Population, 176 JAMA INTERN MED. 55-63 (Jan. 2016), were released more than three
640 years after the *Caronia* decision. Accordingly, the *Caronia* court, in conducting its *Central*
641 *Hudson* evaluation, did not have the benefit of considering the significant findings of this study.
642

643 C. Content- and Speaker-Based Restrictions

644

645 Some have argued that the applicable FDA Authorities are content- and speaker-based
646 restrictions on speech and therefore, under *Sorrell v. IMS Health Inc.*,⁷⁸ heightened scrutiny
647 should be applied. The *Sorrell* court stated, however, that “content-based restrictions on
648 protected expression are sometimes permissible, and that principle applies to commercial
649 speech.”⁷⁹ However, even if the premarket review provisions of the FDA Authorities are
650 characterized as resulting in content- and speaker-based limitations on speech, courts and
651 commentators have recognized that they are appropriate in these circumstances.
652

653 First, when speech is used as evidence to discern intent, a focus on the speech alone will often
654 appear to be speaker- and content-based, but it has not been found to be unconstitutional. For
655 example, in the area of employment discrimination, whether a particular employment action that
656 is otherwise legal is in fact prohibited can depend on whether it was motivated by a prohibited
657 intention. To apply this in any given case, where speech is involved, the trier of fact will
658 necessarily examine the statements of persons who act on behalf of the employer who made the
659 decision and look at the content of those statements to see whether they indicate prohibited
660 intention.⁸⁰ The same principle applies to determining whether a particular act constituted a hate
661 crime – the identity of the speaker and the content of his speech are essential parts of the
662 examination. So too here – whether speech is relevant evidence of a particular intended use will
663 necessarily depend, in part, on the speaker and the content.⁸¹
664

665 Second and alternatively, even if these restrictions on firm activity were viewed as commercial
666 speech restrictions, they are necessarily both speaker- and content-based as part of reasonable

use of the product and provide information for using it safely and effectively for that approved or cleared use. Because the various steps of the *Central Hudson* analysis are connected, the interests at stake necessarily affect the rest of the *Central Hudson* analysis.

⁷⁸ 564 U.S. 552 (2011).

⁷⁹ 564 U.S. at 579. *See also, e.g.*, CTIA -- The Wireless Ass’n v. Berkeley, 139 F. Supp. 3d 1048, 1061 n.9 (N.D. Cal. 2015) (“Ironically, the classification of speech between commercial and noncommercial is itself a content-based distinction. Yet it cannot seriously be contended that such classification itself runs afoul of the First Amendment.”).

⁸⁰ *See, e.g.*, Price Waterhouse v. Hopkins, 490 U.S. 228, 251-52 (1989) (plurality opinion) (finding that, where statute prohibited failure to grant partnership only if that decision was motivated by sexual discrimination, necessary evidence of discrimination could be established based on comments of voting partners).

⁸¹ *See, e.g.*, Christopher Robertson & Aaron S. Kesselheim, *Regulating Off-Label Promotion — A Critical Test*, 375 NEW ENG. J. MED. 2313-15 (Dec. 2016) (“The FDCA’s intent requirement is like innumerable other laws that require juries to determine whether a party had a certain intent when undertaking certain acts. It may be perfectly legal to buy a gun or drive across state lines, but if a defendant’s own speech reveals he or she did so as part of a conspiracy to sell cocaine or a murder-for-hire plot, that speech is routinely used to prove the illegal intent.”).

⁸¹ *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993).

667 government regulation of particular industries in the interest of greater public good.⁸² The law
668 imposes duties and requirements on firms because those firms create the risks and have the
669 knowledge or the ability to acquire knowledge relevant to product risk.⁸³ The relevant
670 provisions of the FDA Authorities are directed to the entities which effectuate product
671 distribution and are best positioned to conduct the research and gather information necessary for
672 premarket review. When emerging and developing scientific data are not yet sufficiently
673 complete or robust to determine safety and efficacy for an unapproved use, reliance on
674 incomplete information could lead (and has led) to adverse results. Premarket review under the
675 FDA Authorities places the burden of uncertainty on the firm by restricting the firm's
676 distribution of its product for that unapproved use, thereby limiting the firm's ability to expose
677 patients to the risks associated with the use – an approach that furthers the substantial
678 government interest in preventing harm to the public health.⁸⁴

679
680 It makes sense for these restrictions to apply only to firms, who have an economic motivation
681 related to product distribution, and not to independent health care providers and researchers.⁸⁵ A
682 broader approach – that, for example, restricted all communication about unapproved uses by
683 both firms and others – would impact more speech and would be less tailored to advancing the
684 various government interests. Thus, focusing on firms who actually control the distribution of
685 the products is an appropriate way to tailor the impact on communications so that it is not more
686 expansive than necessary.
687

⁸² See *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 582-92 (2011) (Breyer, J., dissenting); *United States v. Caronia*, 703 F.3d 149, 180-81 (2d Cir. 2012) (Livingston, J., dissenting). See also *Caronia*, 703 F.3d at 178-179 (Livingston, J., dissenting) (the FDA Authorities do not selectively apply to a certain class of speakers; they apply to all medical product firms, i.e., the industry that has to participate in the premarket review process for that process to function in a manner that protects the public health.).

⁸³ See Christopher Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 551 (2014).

⁸⁴ See, e.g., Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 560-61 (2014) (“In this realm, truth or falsity is not knowable a priori. Any knowledge of truth or falsity emerges from our economic and temporal investments, by those who have incentives to make those investments, in legal and institutional contexts that define those incentives. . . . In this sense, the [FD&C Act] does not exist to police the truth. Instead, the [FD&C Act] exists to provide and protect an epistemic and economic process of research and discovery, one that helps physicians make more rational decisions.”) (citations omitted).

⁸⁵ See, e.g., Christopher T. Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 550-51 (2014) (“It is notable that the [FD&C Act] does not regulate promotion of off-label uses by independent scientists, physicians, advocacy groups, or even laypersons. Such independent information may be more reliable than the self-interested sales pitch of a pharmaceutical representative. More importantly for the law, such independent speakers have no statutory obligations with regard to labeling or distribution of drugs. Thus, their intent that the drug be used off-label is irrelevant. The [FD&C Act] does not regulate mere speech; instead, it regulates the introduction of misbranded drugs into interstate commerce, and it is the intent of the company manufacturing and selling the drug that determines whether the drug is misbranded.”) (citations omitted).

688 D. Alternative Approaches

689
690 FDA has examined alternative approaches suggested, for example, by the court in *United States*
691 *v. Caronia*,⁸⁶ as well as by commentators. Although many of these proposed approaches address
692 one or more of the interests identified above, FDA is concerned that none of them appear to
693 integrate the complex mix of numerous, and sometimes competing, interests at play and thus do
694 not best advance those multiple interests. FDA seeks comment on its review of these
695 alternatives. FDA also seeks comments on other alternatives, as well as comment on how they
696 would advance the multiple interests at play.

697
698 • *Prohibiting altogether the use and/or prescribing of an approved/cleared medical*
699 *product for an unapproved new use.* An outright prohibition on the use of approved/cleared
700 medical products for unapproved uses has been proposed as an alternative because the restriction
701 does not bear directly on speech. This approach would be extremely effective in protecting the
702 government interests in motivating scientifically robust research into unapproved uses and
703 ensuring that new uses of approved/cleared medical products are proven to be safe and effective
704 before they are used to treat patients. However, this prohibition does not take into account the
705 public health interests behind allowing health care providers and patients to work to determine
706 the best treatment options for each patient in specific circumstances.⁸⁷ Viewing FDA’s approach
707 as constitutionally prohibited because this alternative – prohibiting unapproved uses altogether –
708 would impose less restriction on speech relies on a narrow view as to the substantial government
709 interests at stake. This alternative could ultimately injure the audience that is supposed to benefit
710 from the speech.

711
712 • *Barring approval of generics and other affected products until all periods of exclusivity*
713 *on the reference product have expired.* Similarly, with respect to the incentives for innovation
714 provided by the FDA Authorities, such as periods of marketing exclusivity for certain
715 innovations, orphan drugs, and for changes to approved drugs, it has been suggested that, instead
716 of restricting speech of generic (or other affected) manufacturers by preventing them from, for
717 example, promoting their products for exclusivity-protected conditions of use during an
718 innovator product’s period of marketing exclusivity, the FD&C Act could instead be amended to
719 fully bar approval of generic drugs (or other affected products) during any period of exclusivity,
720 including their approval for non-protected conditions of use.⁸⁸ Such an alternative would be
721 contrary to the goal of Congress in enacting the relevant legislation that provides for these
722 periods of exclusivity, which sought to ensure that, on the one hand, brand-name drug
723 manufacturers would have meaningful patent protection and a period of marketing exclusivity to
724 enable them to recover their investments in the development of new drugs, while, on the other
725 hand, ensuring that once applicable patent protection and exclusivity for these new drugs has

⁸⁶ 703 F.3d at 167-68 (2d Cir. 2012).

⁸⁷ See *United States v. Caronia*, 703 F.3d 149, 180 (2d Cir. 2012) (Livingston, J. dissenting) (“[A] ban on off-label prescriptions would . . . constitute an unprecedented intrusion into the practice of medicine, and would result in perhaps an even greater restriction on speech.”). At the public hearing on November 9-10, 2016, several presenters described populations and conditions for which there are few or no approved/cleared medical products. See also *supra* note 54.

⁸⁸ Stephanie M. Greene and Lars Noah, *Debate: Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 264 (2014).

726 expired, consumers would benefit from the rapid availability of lower-priced versions of
727 innovator drugs. Under the regime created by Congress, a generic drug can be approved for
728 fewer than all of the indications for which the brand drug has been approved; generic applicants
729 may carve out from proposed labeling patent or exclusivity-protected conditions of use
730 (including conditions of use protected by three-year Hatch-Waxman exclusivity, orphan
731 exclusivity, or pediatric exclusivity) and obtain approval for the remaining non-protected
732 conditions of use.⁸⁹ Delaying generic entry, including for non-protected conditions of use, is a
733 more restrictive approach than is taken under the current FDA Authorities, and would fail to
734 achieve the goal of ensuring that consumers benefit from lower-priced versions of products once
735 relevant patent or exclusivity protection expires for particular intended uses.

736
737 • *Creating ceilings or caps on the number of prescriptions for an unapproved use.* This
738 proposed approach is similar to the total prohibition on unapproved use above, except that it
739 would allow some amount of prescribing before a ceiling or cap was reached. Once the
740 prohibition was operative, it would present the same problem of limiting health care provider
741 discretion in determining treatments geared toward the needs of each patient. However, before
742 that ceiling was reached, firms could encourage the use of a product for an unapproved use with
743 none of the safeguards of FDA review – just as if there were no requirement of premarket review
744 for a second intended use. Thus, a cut-off of this type does not align with any discernable
745 government interest and would adversely affect the public health. It is also unclear how the
746 ceiling or cap would be determined, and by what public health rationale. If the unapproved use
747 is thought to be potentially harmful for patients, how would one ascertain and justify the number
748 of patients who can be exposed to the unapproved use? And if the unapproved use is thought to
749 be potentially positive, how would one justify denying all other patients access to the product for
750 the unapproved use after the cap is reached? In addition, this approach would be impractical to
751 administer and enforce because, in many cases, it may be difficult to determine for what specific
752 use a health care provider prescribes a product.⁹⁰ Prescriptions written by health care providers
753 do not ordinarily reflect whether a medical product was prescribed for an approved or
754 unapproved use. With certain limited exceptions (for example, in the case of products with
755 significant risks or very high costs where authorization is required prior to dispensing or use), the
756 reason for which a product was prescribed is not available in the data provided to the
757 Government in claims for reimbursement under Medicare or Medicaid.

758
759 • *Limiting Medicare and Medicaid reimbursement to approved uses.* This approach –
760 having the government limit its Medicare and Medicaid reimbursement to approved uses –
761 would again limit health care provider discretion in determining treatments geared toward the
762 needs of patients under Medicare and Medicaid. There would be no governmental interest in
763 virtually eliminating the prescribing of unapproved uses for one subset of the population but
764 having it continue for the remainder of the population (i.e., non-Medicare or -Medicaid patients).
765 And, as in the previous approach, this approach would be impractical to administer and enforce.

⁸⁹ H.R. REP. NO. 98-857, pt.1, at 21.

⁹⁰ See *United States v. Caronia*, 703 F.3d 149, 179-80 (2d Cir. 2012) (Livingston, J. dissenting) (“A ceiling on off-label prescriptions would require collecting data from countless numbers of doctors and patients and, given the medical uncertainties involved, could needlessly (and simultaneously) result in the denial of some effective treatments and the overprescription of ineffective and even dangerous ones.”).

766
767 • *Prohibiting specific unapproved uses that are exceptionally concerning or developing*
768 *tiers based on level of safety concerns with greater regulatory controls for the relatively higher*
769 *risk products.* These approaches would tie the regulatory controls to the degree of safety
770 concerns about the medical product. It bears noting at the outset that without adequate evidence
771 of benefit and risk for the unapproved intended use and some form of premarket review, it is
772 unclear how such a system would operate. Under the first alternative, the government would
773 prohibit specific unapproved uses for medical products that were exceptionally concerning from
774 a safety perspective. The second alternative would similarly tie the applicable regulatory control
775 to the level of safety concern, with stronger controls applied to more dangerous products. Both
776 approaches would be inadequate by themselves to protect the public safety because the required
777 safety assessment depends on the generation of data regarding product dangers before any
778 controls can be applied (and both approaches also ignore the fact that the acceptability of product
779 risks can only be properly evaluated in the context of robust data about the efficacy of the
780 product for the unapproved use so that a determination of whether the benefits of the product for
781 the intended use outweigh its risks can be made). With respect to the less exceptional or lower
782 tier medical products, both approaches would undermine the incentives to engage in premarket
783 review and conduct the necessary research to demonstrate safety and effectiveness, and the
784 incentives for innovation provided by the statutory exclusivity periods discussed above.

785
786 • *Requiring firms to list all potential indications for a product in the initial premarket*
787 *application.* Another proposal is to require manufacturers to list all potential uses in the first
788 application to enable health care providers, the government, and patients to track a medical
789 product's development. However, it is not possible to divine all potential uses of a medical
790 product from an initial study; data and information develop over time through scientific study
791 before and after product approval, as well as product use. If a firm's listing of one or more
792 potential indications, submitted at the same time as the data supporting the primary indication,
793 were the only requirement necessary before firms were allowed to market their product for the
794 claimed indications, this would undermine several government interests listed above, including
795 incentivizing robust research by firms, requiring premarket safety and effectiveness review for
796 each use, developing appropriate instructions for use, and protecting the integrity and reliability
797 of promotional information regarding medical product uses.⁹¹ This alternative would also
798 impact the incentives for innovation provided by the statutory exclusivity periods. This
799 alternative raises additional issues for devices where a firm could seek and receive 510(k)
800 clearance for a device based on one intended use, but then market the product for other intended
801 uses for which FDA has specifically determined that premarket approval is necessary to provide
802 a reasonable assurance of safety and effectiveness.

803

⁹¹ See Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1595 (2014) (“Requiring companies to go on record as to other potential uses of their drug does nothing to eliminate the incentive problem that is created when they are not required to seek FDA approval for those uses in order to promote them without restriction. Nor does it give physicians useful information with which to evaluate off-label uses or promotional communications about off-label uses, or create any mechanisms to protect patients from unsafe prescribing.”).

804 Potential variations on this proposed approach also raise questions. For example, if firms were
805 required to obtain approval/clearance at one time for all intended uses, the initial application
806 might be significantly delayed while new indications were explored. If a firm were unable to
807 seek approval/clearance later for uses that were not identified at the time of an initial application,
808 there would be no incentive to continue scientific exploration that could lead to the development
809 and approval/clearance of new medical treatments. Thus, this approach would negatively impact
810 the public health. For example, Imbruvica (ibrutinib) was approved to treat Mantle Cell
811 Lymphoma in 2013, then for Chronic Lymphocytic Leukemia in 2014. In 2015, it was approved
812 through the breakthrough therapy designation to treat Waldenstrom’s Macroglobulinemia, a rare
813 form of cancer. It is the only product currently approved to treat that disease. Similarly,
814 Rapamune (sirolimus) was initially approved in 1999 as an immunosuppressive agent to help
815 prevent organ rejection. In 2015, it became the first drug to receive approval to treat
816 lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects
817 women of childbearing age.

818
819 • *Allowing firms to actively promote an unapproved use as long as they disclose that the*
820 *use is unapproved and include other appropriate warnings.* This proposed approach would
821 allow firms to undertake active efforts to promote and encourage adoption of the unapproved use
822 as long as they disclose that the use is unapproved and include other appropriate warnings.
823 Warnings and disclosures can help provide material information necessary to assist in
824 understanding data and their value. However, studies show there are limitations to disclosures in
825 terms of the recipients’ perception and understanding.⁹² There is also an inherent contradiction
826 in firms on the one hand promoting a product for an unapproved use while on the other hand
827 disclosing that the product is not approved/cleared for that use (and that the available evidence
828 has not established safety and efficacy for the unapproved use), which further calls into question
829 whether disclosures would be sufficient to prevent harm or deception.⁹³ Furthermore, warnings
830 and disclosures do not protect all of the public health interests advanced by premarket review
831 because this approach would permit firms to bypass the premarket review process for new

⁹² See Aaron S. Kesselheim et al., *Mandatory Disclaimers On Dietary Supplements Do Not Reliably Communicate The Intended Issues*, 34 HEALTH AFFAIRS 438, 445 (2015) (“Our review of the literature indicates that appending disclaimers to ‘free speech’ claims for uses of medications that have not passed scientific muster has not demonstrated sufficient effectiveness to warrant the use of disclaimers on a large scale in the marketing of health care products. We found ample evidence that such disclaimers are often misunderstood or ignored by consumers and had no effect on consumers’ ability to understand messages about health care products and critically evaluate potentially unsupported statements about effectiveness or safety. Thus, the prospect of replacing FDA restrictions on permissible statements for prescription drugs with largely ineffective disclaimers risks returning the pharmaceutical market to a previous era when such inappropriate marketing claims proliferated, to the likely detriment of the public health.”); Aaron S. Kesselheim, *Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 250-51 (2011) (describing inadequacies of disclosures); Christopher Robertson, *The Money Blind: How to Stop Industry Bias in Biomedical Science, Without Violating the First Amendment*, 37 AM. J. L. & MED. 358, 366-69 (2011); Aaron Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1731 (2008).

⁹³ See, e.g., Federal Trade Commission, *FTC Policy Statement on Deception*, (Oct. 14, 1983), at <https://www.ftc.gov/public-statements/1983/10/ftc-policy-statement-deception>; In the Matter of Warner-Lambert Co., 86 F.T.C. 1398, 1414 (1975), *aff’d* Warner-Lambert Co. v. F.T.C., 562 F.2d 749 (D.C. Cir. 1977), *cert denied*, 435 U.S. 950 (1978) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds).

832 intended uses once FDA approves/clears the product for just one use.⁹⁴ Again, in the context of
833 devices, this alternative raises additional issues, as it would allow firms to use the 510(k)
834 pathway for devices based on one intended use and then market the device for different intended
835 uses for which FDA has specifically determined that premarket approval is necessary to provide
836 a reasonable assurance of safety and effectiveness. It would therefore undermine the government
837 interests listed above, including incentivizing robust research by firms, requiring premarket
838 safety and effectiveness review for each use, developing appropriate instructions for use, and
839 protecting the integrity and reliability of promotional information regarding medical product
840 uses. And, if firms do not conduct the research necessary to demonstrate the safety and
841 effectiveness of their products for each intended use, it is unlikely that any other party will have
842 the motivation and resources to undertake it. If disclosures were the only limitation on a firms’
843 ability to distribute a medical product for an unapproved use, we are concerned that it would
844 result in a return to an environment where audiences are faced with a large volume of advertising
845 and promotional labeling claims based on conjecture or extrapolation from limited data, most of
846 which is later found to be false or misleading, but not before misinformation is widely circulated
847 and patients are harmed.⁹⁵ This approach would also undermine the incentives for innovation
848 provided by the statutory exclusivity periods.

849

850 • *Educating health care providers and patients to differentiate false and misleading*
851 *promotion from truthful and non-misleading information.* Although FDA does have several

⁹⁴ See *United States v. Caronia*, 703 F.3d 149, 179 (2d Cir. 2012) (Livingston, J., dissenting) (“A disclaimer system or required listing of intended uses would provide manufacturers much less incentive to submit their drugs for FDA approval, and in turn encourage promotion based on data much less reliable than the clinical investigations required under 21 U.S.C. § 355(d).”).

⁹⁵ See S. REP. NO. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2898, 2901 (“[P]hysicians are regularly inundated with a great mass of advertising and promotional material, much of which is misleading and some actually false. . . .” “Leading physicians testified that it is impossible to keep currently informed of the state of medical knowledge to be found scattered in hundreds of medical journals. . . . Moreover, they stressed that the marketing of a safe but ineffective drug may well be positively injurious to public health. . . . The problem is compounded by the fact that usually a considerable period elapses between the time when a highly-advertised new drug is put on the market and when knowledge becomes widely disseminated among the medical profession that its performance falls seriously short of its claims”). As we reexamine our approach and consider the First Amendment jurisprudence, FDA believes it is critical to avoid a result that “injures the very audience that is supposed to benefit from free speech.” *United States v. Caputo*, 517 F.3d 935, 940 (7th Cir. 2008). FDA seeks to protect against harm to the health and well-being of patients who are not necessarily party to the communications in question. See Constance E. Bagley et al., *Snake Oil Salesmen or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, 23 CORNELL J.L. & PUB. POL’Y 337, 364 (2013) (noting the conceptual distinction between regulating commercial speech “solely for the sake of withholding information” and regulating it to prevent the societal harm resulting from the information’s effect on behavior); Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1592 (2014) (“[I]n seeking to curb the excesses of off-label promotion of medical products to physicians, the FDA seeks to protect not the recipients of the promotion, but their patients. When physicians decide to prescribe a drug for an unapproved use based on a biased presentation of the evidence concerning that use, they put a third party at risk of physical harm. Congress has tasked the FDA with the responsibility to protect the public from unsafe and ineffective drugs. It is not paternalism for the agency to discharge its responsibility in this way.”) (citation omitted).

852 educational resources in this area,⁹⁶ it is unrealistic to suggest that this type of program can be
853 conducted on the scale necessary to effectively combat the adverse impact of the many different
854 ways promotion can be false or misleading.⁹⁷ Even assuming that a large-scale government-
855 sponsored education program was feasible, this approach removes the burden from the seller of
856 the product and puts it on health care providers and patients. Like the preceding proposal, this
857 alternative would allow firms to bypass the premarket review process by marketing or promoting
858 a product for an unapproved use and thereby undermine the substantial government interests in
859 incentivizing robust scientific research, requiring premarket review, developing required labeling
860 that provides appropriate information for safe and effective use, and protecting the integrity and
861 reliability of promotional information regarding medical product uses. This approach would
862 replace the FDA's thorough and rigorous scientific review process with a review of promotional
863 materials by health care providers and patients. Health care providers and patients cannot be
864 expected to acquire the tools, background, and specialized expertise in statistics,
865 pharmacokinetics, biomedical engineering, and other fields that are necessary to conduct a
866 thorough evaluation of the risks and benefits of a new intended use that even roughly approaches
867 that provided by FDA review (assuming that adequate data exist and that all the data are made
868 publicly available), and it is unrealistic to suggest that a government-sponsored education
869 campaign would provide this kind of multi-discipline expertise. In addition, an education
870 campaign would not provide each health care provider or patient with the time needed to conduct
871 such an evaluation of risks and benefits for every use of hundreds of medical products.⁹⁸ This
872 suggested approach also does not account for the possibility that firms may present incomplete or
873 unsubstantiated information, and that the health care provider or consumer would not be well
874 positioned to uncover or weigh the significance of the absence of a full disclosure of all relevant
875 data.⁹⁹

876
877 • *Reminding health care providers of potential malpractice liability.* This proposed
878 approach appears to be suggested as a way of making health care providers more cautious
879 regarding prescribing/using medical products for unapproved uses. To the extent it discourages

⁹⁶ See, e.g., FDA, *Truthful Prescription Drug Advertising and Promotion*, at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm> (last modified Dec. 16, 2016).

⁹⁷ See Aaron S. Kesselheim & Michelle M. Mello, *Health Care Decisions in the New Era of Health Care Reform: Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1593-94 (2014) (“The nation’s experience prior to the 1962 [FD&C Act] amendments amply demonstrated that physicians could not distinguish between truthful and misleading claims of drug efficacy, in part because of misleading promotional statements. Even if didactic strategies for distinguishing among the types of claims made in off-label promotion and understanding the evidence base underlying them could be identified, along with strategies for effectively reaching every physician with this information, it is inconceivable that the government would appropriate funding at a level sufficient to create an effective counterweight to the \$ 50 billion that pharmaceutical companies spend each year on promotion to physicians.”) (citations omitted).

⁹⁸ See Brian S. Alper et al., *How much effort is needed to keep up with the literature relevant for primary care?*, 92 J MED LIBR ASS’N 429-37 (2004) (study on overall workload of systematically keeping up with the medical literature relevant to primary care estimated that it would require 627.5 hours per month).

⁹⁹ See *Bates v. State Bar of Ariz.*, 433 U.S. 350, 383-84 (1977) (holding that limitations on advertising may be appropriate where the public lacks sophistication or a means of verifying information on a particular topic). See also Christopher Robertson, *When Truth Cannot be Presumed: The Regulation of Drug Promotion Under An Expanding First Amendment*, 94 B.U. L. REV. 545, 572 (2014) (“The truth or falsity of the drugmaker’s promotional claims is unknown, largely because the drugmaker has declined to invest in making such a proof.”).

880 all prescribing or use of medical products for unapproved uses by health care providers, this
881 approach would not advance the interests behind allowing health care providers to determine the
882 best treatment options for patients in specific circumstances, such as in treating diseases for
883 which there are no approved treatments or in treating patients for whom all approved treatments
884 have failed. In addition, like the previous example, it would allow firms to bypass the premarket
885 review process for new intended uses and thereby undermine the significant government interests
886 advanced by that process. Furthermore, by essentially shifting the responsibility and perhaps
887 liability from the firm to the health care provider, this approach would not deter firms from
888 developing biased presentations with the potential to mislead the listener.
889

890 • *Taxing firms more heavily for sales of products for unapproved uses than for approved*
891 *uses.* This proposed approach would allow unrestricted sharing of information about unapproved
892 uses of approved/cleared medical products, but attempt to retain some financial incentive for
893 seeking FDA approval by taxing firms' sales for unapproved uses more than sales for approved
894 uses. The proposal does not align with the government interests in part because it would affect
895 all prescribing/use of medical products for an unapproved use equally – whether or not there
896 were circumstances that warranted such prescribing/use.¹⁰⁰ Moreover, it would allow companies
897 to substitute a tax payment for the cost of the robust scientific research needed to protect the
898 public from injuries associated with inadequately studied and tested products. It is not apparent
899 how such tax payments, which could simply become a cost of doing business and/or be directly
900 passed along to patients, would in fact change firms' behavior or otherwise prevent, remedy or
901 deter the significant public health harms that premarket review is designed to avert. This
902 approach would also likely be impractical to administer and enforce because, as noted
903 previously, it may be difficult to determine in many cases the particular use for which a product
904 is being prescribed/used.
905

906 • *Permit promotion of unapproved uses listed in medical compendia.* This proposed
907 approach would rely on medical compendia, which list information about drugs and already list
908 certain unapproved uses of drugs as medically accepted. Medical compendia are developed
909 through many sources, including for-profit individuals or companies and consortiums of
910 recognized academic experts (e.g., the National Comprehensive Cancer Network). All
911 compendia rely on medical literature so their decisions are not based on the same kind of data
912 and information as FDA approval decisions.¹⁰¹ Furthermore, publication bias is a well-known
913 phenomenon, where trials with negative or unfavorable results often are not published, and thus

¹⁰⁰ See Aaron S. Kesselheim, *Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J. L. & MED. 225, 252 (2011) (“[T]axing off-label use would indiscriminately affect evidence-based and non-evidence-based uses. It is also likely that taxation revenue could be incorporated into the price of the drug, and passed on to the consumers or insurers, negating their effect”).

¹⁰¹ Medical publications follow a prescribed format and present salient data and conclusions, but do not provide full, primary datasets to either the reader or to the journal's reviewers. Mike Mitka, *Off-Label Cancer Drug Compendia Found Outdated and Incomplete*, 301 JAMA 1645-1646 (2009) (“Investigators commissioned by the US Centers for Medicare & Medicaid Services (CMS) said compendia of medications used to justify off-label use for cancer treatments appear not to use systematic methods to review or update evidence. As a result, physicians using these compendia to determine treatment regimens for patients with cancer may not be prescribing the best medications for a particular case, and Medicare and other insurers may be paying for suboptimal care for such patients.”).

914 may not be available to developers of compendia.¹⁰² There is also the potential for firms to
915 improperly influence compendia listings.¹⁰³ In contrast, FDA premarket review involves a much
916 more in-depth and unbiased analysis of the underlying data and information. Compendia listings
917 do not rely on this level of detail and are not comparable to an FDA approval.¹⁰⁴ This approach
918 would permit firms to bypass the premarket review process for new intended uses once the
919 product was listed in some compendia. By substituting the criteria used by the various
920 compendia for the FDA premarket review process, this alternative would allow firms to market
921 products for uses that lack robust scientific support and that have not been subject to rigorous
922 scientific review, with the possibility for the introduction of bias. This approach would therefore
923 undermine the government interests listed above, including incentivizing robust research by
924 firms, requiring premarket safety and effectiveness review for each use, developing appropriate
925 instructions for use, and protecting the integrity and reliability of promotional information
926 regarding medical product uses.

927

928 • *Limiting evidence that could be considered relevant to intended use to speech that the*
929 *government can prove is false or misleading.* This approach would limit the type of evidence
930 that could be used to establish the intended use of a product to speech by firms that the
931 government can prove is false or misleading. Under this approach, firms might be free to
932 actively promote unapproved uses of approved/cleared medical products based on incomplete,
933 unbalanced, or non-objective data or information unless and until the government established,
934 after the communication occurred, that the communication was misleading. Essentially, claims
935 would be legal until proven wrong, potentially after patients have been harmed.¹⁰⁵ Such an
936 approach would undermine the current incentives to generate scientific evidence sufficient to
937 establish safety and effectiveness for each intended use of a medical product. For example, the
938 approach would likely incentivize exploratory, small, and less rigorous studies that are more
939 likely to generate positive results. Once a firm has such positive preliminary results, they would
940 be unlikely to perform additional studies to generate reliable evidence of safety or effectiveness.

¹⁰² See *supra* notes 21, 29, 58.

¹⁰³ See, e.g., Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays \$762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), at <https://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal> (“The United States further contends that Amgen used journal articles that were insufficient to support the safety and efficacy of the off-label uses at issue, and improperly obtained listings in medical compendia in an effort to establish that the off-label uses were medically accepted, and thereby eligible for coverage by federal health care programs.”); Angela K. Green et al., *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 JAMA 1541 (2016) (“[T]here is limited transparency about how compendia are assembled or about conflicts of interest on the part of their contributors.”).

¹⁰⁴ See, e.g., Angela K. Green et al., *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 JAMA 1541-1542 (2016) (“A systematic review published in 2009 found that the quality of evidence cited in compendia for off-label cancer drug usage is less rigorous than the standards supporting FDA-approved drugs. This analysis of 14 off-label indications of cancer drugs found substantial limitations in the level, quantity, consistency, and timeliness of evidence among commonly used compendia. Evidence cited by the compendia was often not up-to-date and differed from evidence retrieved through an independent search by the authors. This raises concern that payers may be compelled to cover inadequately proven treatments for which the risks outweigh benefits. Despite the findings of this systematic review, this issue has not been addressed since then.”), citing Amy P. Abernethy et al., *Systematic review: reliability of compendia methods for off-label oncology indications*, 150 ANN. INTERN. MED. 336-343 (2009).

¹⁰⁵ See *supra* note 95.

941 However, many medical products that look promising at early stages of development or clinical
942 testing turn out not to provide any clinical benefit or cause harms when evaluated in larger
943 clinical trials.¹⁰⁶ This approach might even be argued to open the door to statements by a “true
944 believer” who truthfully represents he believes a product cures cancer without any scientific
945 basis for that conclusion. Accordingly, this approach would undermine the requirements for
946 premarket review of medical products for each of their intended uses and undermine all the
947 interests advanced by the premarket review system and related provisions of the FDA
948 Authorities.
949

¹⁰⁶ See, e.g., Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826-1833 (2016) (finding more than half of drugs entering late-stage clinical development fail during or after pivotal clinical trials, primarily because of inadequate efficacy, safety, or both). A few recent examples publicized after the November 9-10, 2016 public hearing of products that initially appeared to show promise but were later found to have safety or efficacy problems include the failure of Eli Lilly’s experimental Alzheimer’s drug, solanezumab, to demonstrate effectiveness and Juno Therapeutics’ decision to place a clinical hold on its experimental leukemia drug following patient deaths. Pam Belluck, *Promising Drug for Alzheimer’s Fails in a Trial*, N.Y. TIMES, Nov. 24, 2016, at A1; Anne Steele, *Juno’s Stock Drops Following Two More Deaths in Cancer-Treatment Trial*, WALL ST. J., Nov. 23, 2016, available at <http://www.wsj.com/articles/junos-stock-drops-following-two-more-deaths-in-cancer-treatment-trial-1479915925>.

950 **APPENDIX A**
951 **SUMMARY OF STATUTORY AND REGULATORY AUTHORITY**
952 **BY PRODUCT CATEGORY**
953

954 The FDA Authorities prohibit the introduction (or causing the introduction) into interstate
955 commerce of a medical product that fails to comply with applicable requirements for approval,
956 licensing, or clearance, or is otherwise misbranded or adulterated. These prohibitions include
957 introducing (or causing the introduction) into interstate commerce of a medical product that is
958 intended for a use that has not been approved or cleared by FDA, even if that same product is
959 approved or cleared for a different use.

960
961 Below is an overview of the legal frameworks governing firms’ communications regarding
962 unapproved uses of medical products, including a discussion of the premarket review processes
963 for each type of medical product. Despite the distinctions in the legal frameworks and associated
964 processes, underlying each are the goals of spurring advances in medicine based on reliable
965 scientific evidence and of ensuring the safety and effectiveness of medical products for each
966 intended use.

967
968 **A. Human Drugs**

969
970 ***1. Premarket Review***

971
972 The FD&C Act requires that all “new drugs” be approved by FDA before they may be
973 distributed in interstate commerce (21 U.S.C. §§ 331(d) and 355(a)). A “new drug” is one that is
974 “not generally recognized, among [qualified] experts . . . as safe and effective for use under the
975 conditions prescribed, recommended, or suggested in the labeling thereof . . .” (21 U.S.C. §
976 321(p)).¹⁰⁷ To obtain FDA approval for a new drug, a sponsor must submit a new drug
977 application (NDA) that demonstrates that its product is safe and effective for each of its intended
978 uses (21 U.S.C. § 355(a)).¹⁰⁸ Safety must be supported by “adequate tests by all methods

¹⁰⁷ The statute qualifies this provision with grandfather clauses that are unlikely to be met by any product marketed today. *See* 21 U.S.C. § 321(p)(1) (certain drugs marketed prior to the 1938 enactment of the FD&C Act) and Pub. L. No. 75-717, 52 Stat. 1040 (certain drugs marketed prior to the enactment of the 1962 amendments to the FD&C Act).

¹⁰⁸ *See also* Wash. Legal Found. v. Henney, 202 F.3d 331, 332 (D.C. Cir. 2000). In addition, the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established an abbreviated new drug application (ANDA) approval process. An ANDA applicant relies on FDA’s previous finding that the reference listed drug (RLD) – a drug previously approved under section 505(c) – is safe and effective. To rely on FDA’s previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA applicant must provide sufficient information to show that the generic drug product has the same active ingredient(s), dosage form, route of administration, and strength as the RLD. An ANDA applicant must also demonstrate that its product has (with certain permissible differences) the same labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve an ANDA unless it finds, among other things, that the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

979 reasonably applicable” (21 U.S.C. § 355(d)(1)). Effectiveness must be supported by substantial
980 evidence, defined in section 505(d)(5) (21 U.S.C. § 355(d)(5)) and further explained in FDA
981 regulations at 21 C.F.R. § 314.126.

982
983 “Substantial evidence” is a rigorous standard that requires scientific data from adequate and
984 well-controlled clinical investigations (*see* 21 U.S.C. § 355(d)). This standard cannot be
985 satisfied by impressions or beliefs of health care providers, reports lacking in details, or personal
986 testimonials.¹⁰⁹

987
988 Even for drugs that are not new drugs, and thus are not subject to the requirements of approval
989 under section 505, safety and effectiveness must be supported by robust scientific evidence. For
990 a drug to achieve “general recognition of safety and effectiveness,” there must be the same
991 quality and quantity of scientific data necessary to support the approval of an NDA, including
992 substantial evidence consisting of adequate and well-controlled clinical investigations that
993 establish the drug as effective.¹¹⁰

994
995 Through its premarket review, FDA determines that a new drug is (or is not) safe for each
996 particular use under the conditions prescribed, recommended, or suggested in the product’s
997 labeling, e.g., dosage, route of administration, contraindications, and warnings.¹¹¹ This
998 assessment requires a use-specific balancing of risks against benefits.¹¹²

999
1000 As part of the process for approving an NDA, FDA also reviews and approves the labeling for
1001 inclusion on or within the package from which the drug is dispensed to help ensure that the
1002 labeling is accurate and conveys important information for the safe and effective use of the
1003 product for its approved use(s). This includes information about a drug’s indications, dosage,
1004 precautions, warnings, and contraindications, as well as other information regarding the efficacy
1005 for each approved use (*see* 21 U.S.C. § 355(b)).¹¹³

1006

¹⁰⁹ *See* *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 618-19, 630 (1973); *see also* 21 C.F.R. § 314.126(e).

¹¹⁰ *See* *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629-631 (1973).

¹¹¹ Under certain circumstances, FDA may also consider additional risks and potential harms in determining whether a drug meets the relevant standard for marketing. For example, FDA may assess the risks of abuse or misuse of certain drugs, or the potential for harm to health from secondary exposure to certain drugs.

¹¹² *See* *United States v. Rutherford*, 442 U.S. 544, 555 (1979) (“Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”).

¹¹³ The labeling that FDA reviews and approves for prescription drugs provides information for prescribers, but also includes information directed to ensuring that patients can use the drug safely and effectively. *See* 21 C.F.R. § 201.100(d)(3) and 21 C.F.R. § 201.57(c)(18) (patient counseling information). Under some circumstances, FDA may also determine that labeling for distribution directly to patients (a medication guide or patient package insert) is necessary as part of a risk evaluation and mitigation strategy (REMS) to mitigate the risks presented by a drug, including a biological product. *See* 21 U.S.C. § 355-1(e)(2). In addition, FDA may require FDA-approved patient labeling if the Agency determines that at least one of these conditions exists: (1) patient labeling could help prevent serious adverse effects; (2) the drug product is one that has serious risk(s) relative to benefit(s), and information concerning the risk(s) could affect patients’ decision to use, or to continue to use, the product; or (3) the drug product is important to health and patient adherence to directions for use is crucial to the drug’s effectiveness. *See* 21 C.F.R. § 208.1.

1007 The Public Health Service Act (PHSA) establishes a premarket approval (referred to as “license”
1008 in the PHSA) process for biological products that is nearly identical to that for new drugs under
1009 the FD&C Act (*see* 42 U.S.C. § 262(i) for the definition of “biological product”). The PHSA
1010 prohibits the interstate distribution of a biological product without FDA approval (42 U.S.C. §
1011 262(a)). A sponsor seeks FDA approval by submitting a biologics license application (BLA) (42
1012 U.S.C. § 262(a)). To obtain approval, the sponsor must demonstrate, among other things, that
1013 the product is “safe, pure, and potent” (42 U.S.C. § 262(a)(2)(C)(i)(I)).¹¹⁴ FDA approves a
1014 biological product for a particular use only when there is sufficient evidence, consisting of
1015 appropriate laboratory tests or controlled clinical data, to show that the product will be safe and
1016 effective for that use when administered in the manner approved (*see* 42 U.S.C. §§ 262(a)(2)(A)
1017 and 262(a)(2)(C)(i)(I); 21 C.F.R. §§ 600.3(p), 600.3(r), 600.3(s), and 601.2(d)). This premarket
1018 review and approval also involves FDA review and approval of the product’s labeling (*see* 21
1019 C.F.R. § 201.56). The standards for approval of biological products are construed similarly to
1020 the standards for approval of new drugs.¹¹⁵

1021 1022 2. Misbranding

1023
1024 All human drugs (including those that are biological products) are subject to the misbranding
1025 provisions of the FD&C Act, which makes it unlawful to misbrand drugs and to distribute
1026 misbranded drugs (21 U.S.C. §§ 331(a), (b), (c), (g), (k), and 352; 21 C.F.R. § 601.5(b)(1)(vi)).
1027 Among other things, a drug is misbranded if its labeling does not contain adequate directions for
1028 use (21 U.S.C. § 352(f)(1)). Adequate directions for use are “directions under which the layman
1029 can use a drug safely and for the purposes for which it is intended” (21 C.F.R. § 201.5). Because
1030 prescription drugs, by definition, are “not safe for use except under the supervision of a
1031 practitioner licensed by law to administer such drug” (21 U.S.C. § 353(b)(1)(A)), the labeling of
1032 a prescription drug cannot provide adequate directions for its safe use by laymen. However,
1033 FDA has exercised its authority under 21 U.S.C. § 352(f) to create regulatory exemptions from
1034 the requirements of section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(2)). Among the
1035 terms that must be met to satisfy these regulatory exemptions, a prescription drug must have
1036 labeling that provides adequate information for its safe and effective use by practitioners for all
1037 the purposes for which it is intended, including all purposes for which it is advertised or
1038 represented (*see* 21 C.F.R. §§ 201.100(c)(1), 201.100(d), 201.56, 201.57, and 201.80). For new
1039 drugs, this labeling also must be approved in an NDA (21 C.F.R. §§ 201.100(c)(2)), 201.100(d),
1040 and 201.115). Thus, an approved prescription drug that is intended for an unapproved use would
1041 be misbranded because the drug does not meet the regulatory exemptions from the requirement
1042 that its labeling bear “adequate directions for use.”

1043

¹¹⁴ A biological product may also be approved as a biosimilar after the firm demonstrates that the product is biosimilar to a biological product (the reference product) that has been shown to be safe, pure, and potent (42 U.S.C. § 262(k)).

¹¹⁵ *See* Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 123(f), 111 Stat. at 2296, 2324 (1997) (codified at 21 U.S.C. § 355 note) (instructing FDA to “minimize differences in the review and approval” of drug and biological products); *see also* FDA, *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, 2-4 (May 1998), at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072008.pdf>.

1044 All drug labeling, as well as advertising for prescription drugs, is subject to additional
1045 misbranding provisions under the FD&C Act. For example, a drug is considered misbranded if
1046 its labeling is “false or misleading in any particular” (section 502(a) of the FD&C Act (21 U.S.C.
1047 § 352(a))). Similarly, a prescription drug is considered misbranded if its advertising fails to
1048 provide a true statement, including information in brief summary, regarding the product’s side
1049 effects, effectiveness and contraindications, or if the advertising is otherwise false or
1050 misleading.¹¹⁶

1051 **B. Animal Drugs**

1052 ***1. Premarket Review***

1053
1054
1055 The FD&C Act and FDA regulations similarly prohibit firms from introducing a “new animal
1056 drug” into interstate commerce for any intended use that FDA has not determined to be safe and
1057 effective. A “new animal drug” is any drug that that is “intended for use for animals other than
1058 man” that is “not generally recognized, among [qualified] experts . . . as safe and effective for
1059 use under the conditions prescribed, recommended, or suggested in the labeling thereof” (21
1060 U.S.C. § 321(v)). A new animal drug includes a drug that has already been approved for one or
1061 more uses and is accompanied by labeling that suggests an unapproved new use; in this situation,
1062 the drug would be an unapproved new drug with respect to that new use and any use of that drug
1063 would be deemed “unsafe” under section 512(a) of the FD&C Act (21 U.S.C. § 360b(a)).
1064

1065
1066 To obtain approval for a new animal drug, a manufacturer must submit a new animal drug
1067 application (NADA) that demonstrates that the product is safe and effective for each of its
1068 intended uses, defined in section 512(d) of the FD&C Act (21 U.S.C. § 360b(d)) and explained in
1069 FDA regulations at 21 C.F.R. part 514. Safety and effectiveness must be established by
1070 “adequate tests by all methods reasonably applicable” that the “drug is safe for use under the
1071 conditions prescribed, recommended, or suggested in the proposed labeling thereof” (21 U.S.C. §
1072 360b(d)(1)(A)).¹¹⁷

1073
1074 Section 201(u) of the FD&C Act provides that “safe” as used in section 512 of the FD&C Act
1075 “has reference to the health of man or animal.” The determination of safety requires FDA to
1076 consider, among other relevant factors, “the probable consumption of such drug and any
1077 substance formed in or on food because of the use of such drug” (21 U.S.C. §360b(d)(2)(A)).
1078 Accordingly, FDA must consider not only the safety of the new animal drug to the target animal,
1079 but, where the new animal drug will be used in animals intended for food, also the safety to
1080 humans of substances formed in or on food as a result of the use of the new animal drug.

1081
1082 The statute further specifies that “substantial evidence” to establish effectiveness for approval
1083 means “evidence consisting of one or more adequate and well controlled investigations. . . by
1084 experts qualified by scientific training and experience to evaluate the effectiveness of the drug

¹¹⁶ See section 502(n) of the FD&C Act (21 U.S.C. § 352(n)) and 21 C.F.R. § 202.1 (prescription drug advertising); see also section 201(n) of the FD&C Act (21 U.S.C. § 321(n)).

¹¹⁷ In addition, the FD&C Act provides other premarket review processes for certain drugs intended for minor species or minor uses in major species. See 21 U.S.C. §§ 360ccc and 360ccc-1.

1085 involved, on the basis of which it could fairly and reasonably be concluded by such experts that
1086 the drug will have the effect it purports or is represented to have under the conditions of use
1087 prescribed, recommended, or suggested in the labeling or proposed labeling thereof” (21 U.S.C.
1088 § 360b(d)(3)).¹¹⁸

1089
1090 As part of the process for approving a new animal drug application, FDA also reviews and
1091 approves the labeling for inclusion on or within the package from which the drug is dispensed to
1092 help ensure that it is accurate and conveys important information related to the safe and effective
1093 use of the product for its intended use(s), such as indications, dosage, withdrawal, precautions,
1094 warnings, and contraindications, as well as information regarding the efficacy for each approved
1095 intended use (*see* 21 U.S.C. § 360b(b)).

1096
1097 One important way that the statutory frameworks applicable to human and animal drugs differ is
1098 that section 512 of the FD&C Act provides that an animal drug is deemed unsafe for any
1099 particular use or intended use of the drug unless there is an approval (or conditional approval or
1100 index listing) for that intended use “and such drug, its labeling, and such use conform to such
1101 approved application” (21 U.S.C. § 360b(a)). Animal drugs that are “unsafe” within the meaning
1102 of section 512(a) of the FD&C Act are adulterated under section 501(a)(5) of the Act (21 U.S.C.
1103 § 351(a)(5)). There is an exception, however, for certain extralabel uses of animal drugs.
1104 Sections 512(a)(4) and (5) provide that such extralabel use will not be considered “unsafe” (and
1105 therefore will not adulterate the new animal drug) when certain conditions are met, and the use
1106 complies with FDA regulations covering the extralabel use.¹¹⁹

1107 1108 **2. Misbranding**

1109
1110 All animal drugs are subject to the misbranding provisions of the FD&C Act, which makes it
1111 unlawful to misbrand drugs and to distribute misbranded drugs (21 U.S.C. §§ 331(a), (b), (c), (g),
1112 (k), and 352). Among other things, a drug is misbranded if its labeling does not contain adequate
1113 directions for use (21 U.S.C. § 352(f)(1)). Adequate directions for use are “directions under
1114 which the layman can use a drug safely and for the purposes for which it is intended” (21 C.F.R.
1115 § 201.5). Because prescription drugs, by definition, are “not safe for animal use except under the
1116 professional supervision of a licensed veterinarian” (21 U.S.C. § 353(f)(1)(A)(i)), the labeling of
1117 a prescription drug cannot provide adequate directions for its safe use by laymen. However,

¹¹⁸ Section 512(d)(3) of the FD&C Act further provides examples of what may constitute an adequate and well-controlled investigation, including a study in a target species, a study in laboratory animals, any field investigation that may be required under section 512 and that meets the requirements of subsection (b)(3) if a presubmission conference is requested by the applicant, a bioequivalence study, or an in vitro study (21 U.S.C. § 360b(d)(3)(A)-(E)).

¹¹⁹ Section 512(a)(4) and (5) of the FD&C Act permit a licensed veterinarian to prescribe an otherwise approved human or animal drug in a manner that is not in accordance with the approved labeling (an “extralabel use”), subject to certain conditions and prohibitions set by regulation (21 U.S.C. § 360b(a)(4)-(5), 21 C.F.R. § 530). This includes, but is not limited to: (1) use in species that are not listed in the labeling; (2) use for indications not listed in the labeling; (3) frequencies, or routes of administration other than those stated in the labeling; and (4) deviation from the withdrawal time indicated on the labeling (21 C.F.R. § 530.3(a)). Such uses are not deemed unsafe for purposes of 512(a)(1), and therefore do not misbrand the drug, provided they are prescribed by and used under the supervision of a licensed veterinarian, and all the provisions of 21 C.F.R. § 530 are followed and the uses are not otherwise prohibited under section 512(a)(4)(D) of the FD&C Act and 21 C.F.R. § 530.25.

1118 FDA has exercised its authority under 21 U.S.C. § 352(f) to create regulatory exemptions from
1119 the requirements of section 502(f)(1) of the FD&C Act. Among the terms that must be met to
1120 satisfy these regulatory exemptions, a prescription new animal drug must be supplied with
1121 labeling that provides adequate information for its safe and effective use by practitioners for all
1122 the purposes for which it is intended, including all purposes for which it is advertised or
1123 represented (*see* 21 C.F.R. § 201.105(c)(1)). For new animal drugs, this labeling also must be
1124 approved in a new animal drug application (21 C.F.R. 201.105(c)(2) and 201.105(d); *see also* 21
1125 C.F.R. § 201.115). Thus, an approved prescription animal drug that is intended for an
1126 unapproved use would be misbranded because the drug does not meet the regulatory exemptions
1127 from the requirement its labeling bear “adequate directions for use.” Further, a use of an
1128 unapproved new animal drug is an “unsafe” use under 512(a), and is therefore adulterated as well
1129 as misbranded (21 U.S.C. §§ 360b(a) and 351(a)(5)).

1130
1131 All new animal drug labeling, as well as advertising for prescription drugs, is subject to
1132 additional misbranding provisions under the FD&C Act. For example, a drug is considered
1133 misbranded if its labeling is “false or misleading in any particular” (section 502(a) of the FD&C
1134 Act (21 U.S.C. § 352(a))). Similarly, a prescription drug is considered misbranded if its
1135 advertising fails to provide a true statement – including information in brief summary regarding
1136 the product’s side effects, effectiveness, and contraindications – or if its advertising is otherwise
1137 false or misleading.

1138 **C. Devices Intended for Use in Humans**¹²⁰

1139 **1. Classification System and Premarket Review**

1140
1141
1142
1143 As discussed further below, a device is adulterated or misbranded if, among other things, it is
1144 intended for a use that has not been approved or cleared by FDA even if that same product is
1145 approved or cleared for a different use. The type of premarket review pathway is determined by
1146 the degree of review and regulation that FDA deems necessary to provide a reasonable assurance
1147 of safety and effectiveness for a given device type. Although the premarket submission review
1148 pathways (e.g., approval application (PMA), *de novo*, and 510(k)) differ in various ways, they all
1149 fit within the same regulatory framework that enables FDA to ensure that devices on the market
1150 are ones that have been determined by FDA to have a reasonable assurance of safety and
1151 effectiveness for each and every use for which they are intended.

1152 **a. Class System**

1153
1154
1155 The Medical Device Amendments of 1976 (Pub. L. No. 94-295) directed FDA to issue
1156 regulations that classify all devices that were in commercial distribution at that time into one of
1157 three regulatory control categories: class I,¹²¹ class II,¹²² or class III,¹²³ depending upon the

¹²⁰ Premarket review requirements do not apply to devices intended for use solely in animals.

¹²¹ Class I devices are subject to a comprehensive set of regulatory authorities called general controls that are applicable to all classes of devices (*see* section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A))). General controls apply to all three classes of medical devices; however, they are the only level of controls that apply to class I devices. General controls are described in sections 501 (adulterated devices), 502 (misbranded devices),

1158 degree of regulation necessary to provide reasonable assurance of their safety and effectiveness,
1159 with class I requiring the least regulation and class III requiring the most regulation.¹²⁴

1160
1161 Devices that were not in commercial distribution prior to the Medical Device Amendments of
1162 1976 are automatically classified under section 513(f)(1) of the FD&C Act into class III without
1163 any FDA rulemaking process. Those devices remain in class III and require premarket approval
1164 (discussed below) unless and until any such device is classified into class I or II under section
1165 513(f)(2) or (f)(3) of the FD&C Act or FDA issues an order finding the device to be substantially
1166 equivalent (also discussed below), in accordance with the criteria in section 513(i) of the FD&C
1167 Act, to a legally marketed (predicate) device that does not require premarket approval (see
1168 sections 510(k), 513(f)(1)(A), and 513(i) of the FD&C Act).

1169
1170 Classification determinations must be based on an evaluation of the safety and effectiveness of
1171 the device considering (1) the persons for whose use the device is intended; (2) the intended
1172 conditions of use prescribed, recommended, or suggested in the labeling of the device; and (3)
1173 the probable benefits of the device as compared with the probable risks of its use.¹²⁵

1174
1175 Moreover, the effectiveness and safety of the device must be determined on the basis of valid
1176 scientific evidence as set forth in section 513(a)(3) of the FD&C Act (21 U.S.C. § 360c(a)(3))
1177 and further explained in FDA regulations at 21 C.F.R. § 860.7. “Valid scientific evidence” is
1178 evidence from well-controlled investigations, partially controlled studies, studies and objective
1179 trials without matched controls, well-documented case histories conducted by qualified experts,
1180 and reports of significant human experience with a marketed device, from which it can fairly and

510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports on devices),
and 520 (general provisions respecting control of devices intended for human use) of the FD&C Act.

¹²² Class II devices are devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls necessary to provide such assurance (*see* section 513(a)(1)(B) of the FD&C Act (21 U.S.C. § 360c(a)(1)(B))). Special controls are device-specific and include performance standards, post-market surveillance, patient registries, special labeling requirements, premarket data requirements, and guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act).

¹²³ Class III devices are devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device (*see* section 513(a)(1)(C) of the Act (21 U.S.C. § 360c(a)(1)(C))).

¹²⁴ This class system was intended to provide assurances of public health to patients and health care providers while not stifling device innovation: “After lengthy hearings and careful consideration, the Committee has developed a balanced regulatory proposal intended to assure that the public is protected from unsafe and ineffective medical devices, that health professionals have more confidence in the devices they use or prescribe, and that innovations in medical device technology are not stifled by unnecessary restrictions. The bill makes distinctions between those devices which are simple in design and represent little risk to health and those which are sophisticated and potentially hazardous.” H.R. REP. NO. 94-853, at 12 (1976). Also, with respect to determining the regulatory status of a device, the legislative history of the FD&C Act states that “there may be instances in which a particular device is intended to be used for more than one purpose. In such instances, it is the Committee’s intention that each use may, at the Secretary’s discretion, be treated as constituting a different device for purposes of classification and other regulation.” *Id.* at 14-15.

¹²⁵ *See* sections 513(a)(2) and (b) of the FD&C Act (21 U.S.C. §§ 360c(a)(2) and (b)); 21 C.F.R. § 860.7.

1181 responsibly be concluded by qualified experts that there is a reasonable assurance of the safety
1182 and effectiveness of a device under its conditions of use.¹²⁶

1183
1184 There is reasonable assurance that a device is safe when it can be determined, based upon valid
1185 scientific evidence, that the probable benefits to health from use of the device for its intended
1186 uses and conditions of use, when accompanied by adequate directions and warnings against
1187 unsafe use, outweigh any probable risks.¹²⁷ Further, there is reasonable assurance that a device
1188 is effective when it can be determined, based upon valid scientific evidence, that in a significant
1189 portion of the target population, the use of the device for its intended uses and conditions of use,
1190 when accompanied by adequate directions for use and warnings against unsafe use, will provide
1191 clinically significant results.¹²⁸

1192
1193 For example, when classifying *in vitro* diagnostic (IVD) devices,¹²⁹ FDA reviews the analytical
1194 and clinical performance information to evaluate the benefits and risks of the test and to
1195 determine whether the test will provide clinically significant results.

1196
1197 The class into which a device is placed reflects the level of premarket review necessary to
1198 provide a reasonable assurance of safety and effectiveness.

1199
1200 b. PMA, *De Novo*, and 510(k) Premarket Submissions

1201
1202 PMA approval is required by FDA before most class III devices can be legally marketed. PMA
1203 approval is based on a determination by FDA that the PMA contains sufficient valid scientific
1204 evidence¹³⁰ to assure that the device is safe and effective for its intended use(s). The PMA
1205 includes sections containing, among other things, technical data, non-clinical laboratory studies,
1206 and clinical investigations. Before approving or denying a PMA, the appropriate FDA advisory
1207 committee may review the PMA at a public meeting and provide FDA with the committee's
1208 recommendation on whether FDA should approve the submission. After FDA notifies the
1209 applicant that the PMA has been approved or denied, a notice is published on the Internet (1)
1210 announcing the data on which the decision is based, and (2) providing interested persons an
1211 opportunity to petition FDA within 30 days for reconsideration of the decision.¹³¹

1212
1213 For devices subject to PMA approval, labeling is reviewed and approved by FDA as part of the
1214 PMA review (*see* section 515(c)(1)(F) of the FD&C Act (21 U.S.C. § 360e(c)(1)(F))).

1215

¹²⁶ See 21 C.F.R. § 860.7(c)(2). Sufficiently relevant and reliable real-world data could constitute valid scientific evidence, depending on the characteristics of the data, and may be appropriate for use in support of a premarket submission.

¹²⁷ See 21 C.F.R. § 860.7(d). The valid scientific evidence used to determine the safety of a device must adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

¹²⁸ See 21 C.F.R. § 860.7(e).

¹²⁹ See 21 C.F.R. § 809.3(a).

¹³⁰ See 21 C.F.R. § 860.7(c)(2).

¹³¹ See section 515(d) of the FD&C Act (21 U.S.C. § 360e(d)); 21 C.F.R. part 814 subpart C ("FDA Action on a PMA").

1216 Devices of a new type that FDA has not previously classified based on the criteria at section
1217 513(a)(1) of the FD&C Act and that are automatically classified into class III by operation of
1218 law, may be classified into class I or class II under the *de novo* process. If a sponsor believes its
1219 device is appropriate for classification into class I or class II and determines there is no predicate
1220 device, the submitter may submit a *de novo* request for classification¹³² as the premarket
1221 submission in which the submitter provides information to demonstrate that general controls or
1222 general and special controls are sufficient to provide a reasonable assurance of safety and
1223 effectiveness for the device. FDA may decline to classify a device that is not of low-moderate
1224 risk or for which general controls would be inadequate to control the risks and special controls to
1225 mitigate the risks cannot be developed.

1226
1227 If the submitter demonstrates that general controls, or a combination of general and special
1228 controls, are sufficient to provide a reasonable assurance of safety and effectiveness, FDA will
1229 grant the *de novo* request for classification and issue a written order classifying the specific
1230 device and device type in class I or class II. The device is granted marketing authorization
1231 subject to general controls and any identified special controls, and may serve as a predicate for
1232 future 510(k) submissions. FDA will publish a notice in the *Federal Register* announcing the
1233 classification and the regulatory controls necessary to provide a reasonable assurance of safety
1234 and effectiveness. FDA will also publish a decision summary on the FDA website, which
1235 provides an overview of the data in support of the *de novo* submission.¹³³

1236
1237 Devices granted marketing authority under *de novo* requests should be sufficiently understood to
1238 explain all the risks and benefits of the device such that all risks can be appropriately mitigated
1239 through the application of general controls or general and special controls to provide reasonable
1240 assurance of safety and effectiveness. Further, since devices classified under *de novo* requests
1241 may serve as predicates for future devices which can be appropriately regulated through the
1242 510(k) pathway, FDA carefully considers the benefit-risk profile of these devices in the
1243 determination that there is reasonable assurance of safety and effectiveness.

1244
1245 Accordingly, if insufficient information exists to determine that general controls or general and
1246 special controls would provide reasonable assurance of safety and effectiveness for the device,
1247 the device cannot be classified as a class I or II device. Such a device would generally be subject
1248 to PMA review.¹³⁴

1249 The 510(k) review standard (substantial equivalence of a new device to a predicate device)
1250 differs from the PMA and *de novo* review standards. The 510(k) review standard is comparative,

¹³² See section 513(f)(2) of the FD&C Act (21 U.S.C. § 360c(f)(2)).

¹³³ Further information about decision summaries can be found on FDA's website, *Evaluation of Automatic Class III Designation (De Novo) Summaries*, at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm> (last updated Dec. 22, 2016).

¹³⁴ See section 513(a)(1)(C) of the FD&C Act (21 U.S.C. § 360c(a)(1)(C)). See also section 513(f)(2)(A)(iv) of the FD&C Act (21 U.S.C. § 360c(f)(2)(A)(iv)) (stating that FDA has the authority to decline to undertake a classification request under the *de novo* pathway if FDA determines, among other things, that "the device submitted is not of low-moderate risk or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.").

1251 whereas the PMA and *de novo* review standards rely on an independent demonstration of safety
1252 and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial
1253 equivalence determination in every 510(k) review.¹³⁵ The standard for a determination of
1254 substantial equivalence in a 510(k) review is set out in section 513(i) of the FD&C Act (21
1255 U.S.C. § 360c(i)).^{136,137}
1256

1257 During the 510(k) review, FDA considers the device’s safety and effectiveness in its substantial
1258 equivalence determination (as discussed more fully below), and also in its evaluation of
1259 compliance with any applicable special controls, which FDA has determined to be necessary to
1260 provide a reasonable assurance of safety and effectiveness for the device type.
1261

1262 Safety and effectiveness are considered in two parts of the FDA’s substantial equivalence
1263 review. First, FDA must find that the intended use of the device and its predicate are “the same.”
1264 Under section 513(i)(1)(E)(i) of the FD&C Act (21 U.S.C. § 360c(i)(1)(E)(i)), for the purposes
1265 of substantial equivalence review, “[a]ny determination by the Secretary of the intended use of a
1266 device shall be based upon the proposed labeling submitted in a report for the device under
1267 section 510(k).”
1268

1269 When a review of the indications for use and all other information in the proposed labeling
1270 submitted with a 510(k) supports an intended use that is the same as that of the predicate device,
1271 FDA will determine that the new device and predicate device have the same intended use.
1272 When a review of the labeling submitted with a 510(k) shows that the indications for use of a
1273 new device and predicate device differ, FDA must evaluate whether the new indications for use
1274 fall within the same intended use as that of the predicate device. In such cases, FDA determines

¹³⁵ The legislative history of the Medical Device Amendments of 1976 indicates that: “The term ‘substantially equivalent’ is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The Committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness.” H.R. REP. NO. 94-853, at 36 (1976).

¹³⁶ Section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)) states that:

(i)(1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device –

(i) has the same technological characteristics as the predicate device, or

(ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

(B) For purposes of subparagraph (A), the term “different technological characteristics” means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

¹³⁷ In the Safe Medical Devices Act of 1990 (SMDA) (Pub. L. No. 101-629), Congress defined substantial equivalence in section 513(i) of the FD&C Act and required FDA to evaluate whether a new device is as safe and effective as a predicate device when there are technological differences between the devices.

1275 the indications for use of the new device based upon review of the proposed labeling, and then
1276 may rely upon relevant clinical or scientific information that does not appear in the proposed
1277 labeling submitted with the 510(k) regarding the safety and effectiveness of the new indications
1278 for use.¹³⁸ Clinical data provided in support of any marketing application, including a 510(k)
1279 when those data are relevant to a substantial equivalence determination, should constitute valid
1280 scientific evidence as defined in 21 C.F.R. § 860.7(c)(2). Provided it constitutes valid scientific
1281 evidence, such data may include a: randomized, multi-arm, “blinded” study with concurrent
1282 sham (placebo) control; randomized, multi-arm, “blinded” study with concurrent (“active”)
1283 control; non-randomized study with concurrent (“active”) control; single-arm study with patient
1284 serving as own control; single-arm study with historical control (using patient-level data); single-
1285 arm study with literature control (historical control); single-arm study with objective
1286 performance criteria; single-arm study with performance goals; registry; observational study;
1287 systematic review (meta-analysis with patient-level data); meta-analysis based on summary
1288 information only; or literature summary.

1289
1290 Second, when comparing a new device to a predicate device, FDA must find that the two devices
1291 have “the same technological characteristics,” or that a “significant change in the materials,
1292 design, energy source or other features of the device” does not raise different questions of safety
1293 and effectiveness and that the device is as safe and effective as the legally marketed predicate
1294 device.¹³⁹

1295
1296 When evaluating whether a new device is as safe and effective as a predicate device, if the risks
1297 associated with the new device increase as compared to the predicate device, as explained in
1298 draft guidance,¹⁴⁰ FDA may still determine that the new device is substantially equivalent to the
1299 predicate device if, for example, FDA finds from a review of the new device’s performance data
1300 that there are also increased benefits with the new device as compared to the predicate device.
1301 When looking at the increased risks posed by the new device, FDA may consider the degree of
1302 risk in comparison to the predicate device. FDA may also consider whether additional measures
1303 may help mitigate the increased risks. Depending on the increase in risk of the new device as
1304 compared to the predicate device, FDA may determine that the new device is not substantially
1305 equivalent to the predicate device, even despite increased benefits of the new device.

1306
1307 Although the 510(k) process involves a comparison of a new device to a predicate device rather
1308 than an independent demonstration of the new device’s safety and effectiveness, as is required
1309 for a PMA and a *de novo* submission, in all these cases FDA’s review process reflects a

¹³⁸ See section 513(i)(1)(A)(ii)(I) of the FD&C Act (21 U.S.C. § 360c(i)(1)(A)(ii)(I)); 21 C.F.R. § 807.100(b). See also FDA, *The 510(k) Process: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]*, Guidance for Industry and Food and Drug Administration Staff (July 2014) at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>.

¹³⁹ See section 513(i)(1) of the FD&C Act (21 U.S.C. § 360c(i)(1)).

¹⁴⁰ See FDA, *Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics*, Draft Guidance for Industry and Food and Drug Administration Staff, 6 (July 2014), at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773.pdf>. This draft guidance, when finalized, will represent FDA’s current thinking on this topic.

1310 determination of the level of control necessary to provide a “reasonable assurance of safety and
1311 effectiveness.” The evidentiary standard, however, is different. In the 510(k) context, FDA
1312 generally relies, in part, on FDA’s prior determination that a reasonable assurance of safety and
1313 effectiveness exists for the predicate device. Demonstrating basic similarities between a new
1314 device and a predicate device typically requires manufacturers to provide descriptive information
1315 such as a comparison of specifications, materials, and technology. In contrast, FDA generally
1316 evaluates differences between the new device and the predicate device to determine their effect
1317 on safety and effectiveness. It follows that the evidence necessary to show substantial
1318 equivalence will increase as differences between the new device and the predicate device
1319 increase if those differences significantly affect, or may significantly affect, safety or
1320 effectiveness (21 C.F.R. § 807.81).

1321
1322 FDA has determined that certain low-risk class I and class II devices do not require a 510(k) to
1323 provide a reasonable assurance of safety and effectiveness. These devices are said to be “510(k)
1324 exempt.” These devices are exempt from complying with 510(k) requirements subject to certain
1325 limitations; however, they are not exempt from certain general controls. For example, 510(k)-
1326 exempt devices must:

- 1327
- 1328 • be suitable for their intended use
- 1329
- 1330 • be adequately packaged and properly labeled
- 1331
- 1332 • have establishment registration and device listing forms on file with FDA
- 1333
- 1334 • be manufactured under a quality system (with the exception of a small number of class I
- 1335 devices that are subject only to complaint files and general recordkeeping requirements)
- 1336

1337 ***2. Adulteration and Misbranding***

1338

1339 The FD&C Act prohibits the introduction (or causing the introduction) into interstate commerce
1340 of an adulterated or misbranded device.

1341
1342 As discussed above, firms must obtain approval of a PMA for certain high risk, class III devices
1343 before introducing the device into interstate commerce (*see* sections 501(f)(1), 513, and 515 of
1344 the FD&C Act (21 U.S.C. §§ 351(f)(1), 360c, and 360e) and 21 C.F.R. §§ 814.20 and 814.39) or
1345 before introducing an already approved device into interstate commerce with the intent of
1346 marketing it for a new use. A device that lacks the necessary PMA approval is adulterated under
1347 section 501(f)(1)(B)(i) of the FD&C Act (21 U.S.C. § 351(f)(1)(B)(i)).

1348
1349 For most moderate-risk class I and class II devices, firms must obtain 510(k) clearance before
1350 introducing the device into interstate commerce, and before making a major change or
1351 modification in the intended use of a cleared device (*see* sections 502(o) and 510(k) of the
1352 FD&C Act (21 U.S.C. §§ 352(o) and 360(k)) and 21 C.F.R. § 807.81(a)(3)(ii)).¹⁴¹ A device is

¹⁴¹ Devices that are exempt from premarket notification requirements, generally because they are low risk, may be introduced into interstate commerce for the specifically exempt intended use(s) without obtaining FDA clearance

1353 misbranded under section 502(o) of the FD&C Act (21 U.S.C. § 352(o)) if the firm fails to notify
1354 the Agency of the intent to introduce the device into commercial distribution as required by
1355 section 510(k) of the Act (21 U.S.C. § 360(k)). Additionally, a device that lacks the necessary
1356 510(k) clearance is considered by operation of law to be a class III device that needs an approved
1357 PMA, and thus also is adulterated under section 501(f)(1)(B)(i) of the FD&C Act (21 U.S.C.
1358 § 351(f)(1)(B)(i)).

1359
1360 For certain low-risk class I and class II devices, firms are exempt from 510(k) clearance as long
1361 as, among other things, the device is for the same intended use as a legally marketed device of
1362 that generic type (*see* section 510(m)(2) of the FD&C Act (21 U.S.C. § 360(m)(2))). A 510(k)-
1363 exempt device that is marketed for an intended use not included in the regulation classifying that
1364 generic device type is no longer 510(k)-exempt and is an adulterated, unapproved class III device
1365 under section 513(f)(1) of the FD&C Act (21 U.S.C. § 360c(f)(1)).

1366
1367 The labeling and advertisement of devices also are subject to misbranding provisions under the
1368 FD&C Act. A device is misbranded if its labeling is “false or misleading in any particular”
1369 (section 502(a) of the FD&C Act (21 U.S.C. § 352(a))). Moreover, a restricted device¹⁴² is
1370 considered misbranded if its advertising fails to provide adequate information regarding the
1371 product’s safety and effectiveness, or is otherwise false or misleading (*see* sections 502(q) and
1372 (r) of the FD&C Act (21 U.S.C. § 352(q) and (r)); *see also* section 201(n) of the FD&C Act (21
1373 U.S.C. § 321(n))).

1374

(*see* sections 510(l) and (m) of the FD&C Act (21 U.S.C. § 360(l) and (m))). These devices, however, still remain subject to certain general controls such as labeling requirements and other post-market provisions of the FD&C Act. Changing the intended use of such a device generally requires 510(k) clearance and may, in certain situations, require a PMA.

¹⁴² Under section 520(e) of the FD&C Act (21 U.S.C. § 360j(e)), the FDA is authorized to restrict the sale, distribution, or use of a device if there cannot otherwise be reasonable assurance of its safety and effectiveness. A restricted device can only be sold on oral or written authorization by a licensed practitioner or under conditions specified by regulation.

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APPENDIX B
EXAMPLES WHERE COMMONLY ACCEPTED UNAPPROVED USES HAVE LED
TO PATIENT HARM

A. Erythropoiesis Stimulating Agents (ESAs)

People with anemia have lower than normal amounts of circulating red blood cells, which contain hemoglobin that carries oxygen to body tissues. Anemia causes fatigue and shortness of breath, which adversely affects a person’s ability to perform even normal daily activities. Health care providers often treat severe anemia with red blood cell transfusions.¹⁴³

Erythropoiesis-Stimulating Agents (ESAs) (which include Epoetin alfa (marketed as Procrit, Epogen) and Darbepoetin alfa (marketed as Aranesp)) work by stimulating the bone marrow to produce red blood cells. They are currently approved for the treatment of anemia resulting from chronic kidney disease (CKD), chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), and also to reduce the number of blood transfusions during and after certain major surgeries.

ESAs have been widely used to treat anemia of cancer, regardless of whether or not a patient was undergoing chemotherapy, and have also been in nonanemic cancer patients undergoing chemotherapy and at dosing schedules other than those approved by FDA. At least the unapproved use for anemia of cancer was listed as a “medically-accepted indication” in one of the compendia used to determine coverage for certain federal health care programs.¹⁴⁴

Subsequently, controlled trials of unapproved use of ESAs revealed decreased survival in cancer patients receiving ESAs and increased risks of cancer relapse.¹⁴⁵ FDA added a boxed warning to ESA products to warn about increased mortality and tumor progression for patients with cancer treated with ESAs. The warning also noted increased risk of serious cardiovascular events and thromboembolic events.

B. Atypical Antipsychotics

Most atypical antipsychotic drugs are approved for treatment of schizophrenia and bipolar disorder. However, they have been commonly used for the unapproved use of treating behavior problems in elderly patients with dementia. Subsequent controlled trials have revealed increased

¹⁴³ See Sanjeev Sharma et al., *Transfusion of Blood and Blood Products: Indications and Complications*, 83 AM. FAM. PHYSICIAN 719 (2011).

¹⁴⁴ See *Erythropoiesis-Stimulating Agents: Continued Challenges*, 3 J. ONCOL. PRAC. 248 (2007).

¹⁴⁵ See Julia Bohlius et al., *Erythropoietin or Darbepoetin for Patients with Cancer – meta-analysis based on individual patient data (Review)*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS, 3:CD007303 (2009); Brian Leyland-Jones et al., *Maintaining Normal Hemoglobin Levels with Epoetin Alfa in Mainly Nonanemic Patients with Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study*, 23 J. CLIN. ONCOL. 5960 (2005); Michael Henke et al., *Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial*, 362 LANCET 1255 (2003); *Erythropoiesis-Stimulating Agents: Continued Challenges*, 3 J. ONCOL. PRAC. 248 (2007).

1411 mortality resulting from this use, primarily resulting from deaths due to cardiovascular events
1412 and infectious disease.¹⁴⁶ These products now bear a boxed warning noting the risks of using
1413 them to treat elderly patients with dementia.

1414

1415 C. Premarin/Prempro

1416

1417 Starting in the 1980s and continuing through the 1990s, estrogen use steadily increased among
1418 women, in part due to publication of numerous reports presenting observational evidence
1419 suggesting a lower incidence of coronary heart disease in estrogen users.¹⁴⁷ During this time,
1420 doctors extensively prescribed the estrogen drug Premarin and the estrogen plus progestin drug
1421 Prempro for long-term use in women in the hope of preventing the increased risk of coronary
1422 heart disease that follows menopause.¹⁴⁸

1423

1424 FDA first approved Wyeth Pharmaceutical's estrogen product, Premarin, to treat menopausal
1425 symptoms, including severe hot flashes, in 1942.¹⁴⁹ In 1995, FDA approved Wyeth
1426 Pharmaceuticals' estrogen plus progestin drug, Prempro, to treat menopausal symptoms and
1427 prevent postmenopausal osteoporosis.¹⁵⁰ However, FDA did not approve any estrogen products
1428 to prevent coronary heart disease or other chronic diseases as no manufacturer produced
1429 evidence showing such drugs were safe and effective for this use.¹⁵¹

1430

1431 In 1997, when use of Premarin and Prempro to treat coronary artery disease was finally studied
1432 as part of the Women's Health Initiative (WHI) – a large government-sponsored randomized
1433 placebo-controlled trial – results showed these drugs increased risks of adverse health events in
1434 women.¹⁵² Results of the Prempro study showed an increased risk of breast cancer, heart attack,
1435 stroke, blood clots in the lungs and legs, and dementia in women using Prempro when compared
1436 to a placebo group.¹⁵³ Given this conclusion, WHI halted the planned 8-year study after just 5

¹⁴⁶ See, e.g. Donovan T. Maust et al., *Antipsychotics, Other Psychotropics, and the Risk of Death in Patients with Dementia: Number Needed to Harm*, 72 JAMA PSYCHIATRY 438-445 (2015).

¹⁴⁷ Marcia L. Stefanick, *Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration*, 118 AM. J. MED. 64, 67 (2005).

¹⁴⁸ Declaration of Rachel E. Sherman, MD, Par Pharmaceutical, Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

¹⁴⁹ In 1986, FDA also announced that Premarin was effective for prevention of osteoporosis in postmenopausal women. See FDA, *Conjugated Estrogens - Letter from Dr. Janet Woodcock*, (May 5, 1997), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm168836.htm>.

¹⁵⁰ FDA, *Drugs@FDA.gov: FDA Approved Drug Products Prempro (estrogens, conjugated; medroxyprogesterone acetate) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=020527> (last visited Dec. 20, 2016).

¹⁵¹ FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm>.

¹⁵² FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm>; National Institutes of Health, *WHI Study Finds No Heart Disease Benefit, Increased Stroke Risk With Estrogen Alone*, (Apr. 13, 2004), at <https://www.nhlbi.nih.gov/news/press-releases/2004/whi-study-finds-no-heart-disease-benefit-increased-stroke-risk-with-estrogen-alone>.

¹⁵³ FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm>.

1437 years and recommended that doctors not prescribe Prempro to postmenopausal women for
1438 cardiovascular protection.¹⁵⁴ WHI also halted the Premarin study early after finding an increased
1439 risk of stroke and blood clotting in women using Premarin when compared to a placebo group.¹⁵⁵
1440 After reviewing the WHI findings and recommendations, the Data and Safety Monitoring
1441 Board¹⁵⁶ for the trial concluded that, given the risks of the drug, Premarin was not a viable
1442 intervention for prevention of chronic diseases, including prevention of chronic heart disease.¹⁵⁷
1443
1444 After release of the WHI study results, FDA issued a statement encouraging manufacturers to
1445 revise estrogen- and progestin-containing drug labels to reflect the risks of unapproved use.¹⁵⁸
1446 By January 2003, FDA and Wyeth revised Premarin and Prempro's labeling to include a boxed
1447 warning stating that estrogens and estrogen-plus-progestin therapies should not be used for
1448 prevention of cardiovascular disease.¹⁵⁹ FDA also released a guidance document reporting the
1449 results of the WHI study, encouraging drug sponsors to seek FDA approval of estrogen drugs
1450 only at the lowest doses and exposures possible, and warning against unapproved use of Prempro
1451 and Premarin.¹⁶⁰ In 2005, FDA published a second guidance document recommending labeling
1452 changes for estrogen drug products, including revising Patient Information leaflets with
1453 information about possible side effects and a clear warning to not use estrogen drugs to reduce
1454 risks associated with heart disease, such as heart attacks or strokes.¹⁶¹ FDA has also modified
1455 the approved indications for Premarin and Prempro to clarify that these drugs should only be

¹⁵⁴ Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321, 325 (2002); FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm>.

¹⁵⁵ National Institutes of Health, *WHI Study Finds No Heart Disease Benefit, Increased Stroke Risk With Estrogen Alone*, (Apr. 13, 2004), at <https://www.nhlbi.nih.gov/news/press-releases/2004/whi-study-finds-no-heart-disease-benefit-increased-stroke-risk-with-estrogen-alone>.

¹⁵⁶ The Data and Safety Monitoring Board is a committee of experts, with no vested interest in a specific treatment, who are responsible for reviewing ongoing trial data and ensuring the safety of human subjects enrolled in the clinical trials. Data and Safety Monitoring Boards are required for multi-site clinical trials with interventions that entail risk(s) to participants. See U.S. Department of Health and Human Services, *Data and Safety Monitoring Boards in NIH Clinical Trials: Meeting Guidance, But Facing Some Issues*, (June 2013), at <http://osp.od.nih.gov/sites/default/files/resources/oei-12-11-00070.pdf>.

¹⁵⁷ Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321, 325 (2002).

¹⁵⁸ FDA, *FDA Statement on the Results of the Women's Health Initiative*, (Aug. 13, 2002), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm>; FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm>.

¹⁵⁹ FDA, *Prempro/Premphase (conjugated estrogens/medroxyprogesterone acetate tablets)*, at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153358.htm> (last updated Aug. 20, 2013).

¹⁶⁰ FDA, *Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation* (Jan. 2003), at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135338.pdf>.

¹⁶¹ FDA, *Draft Guidance for Industry, Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling* (Nov. 2005), at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135336.pdf>.

1456 used when the benefits clearly outweigh the risks and advised health care providers to prescribe
1457 these drugs to women at the lowest dose and shortest duration possible.¹⁶²

1458

1459 **D. Tambocor and Enkaid**

1460

1461 FDA approved the antiarrhythmic drugs Tambocor (flecainide), manufactured by 3M
1462 Pharmaceuticals, and Enkaid (encainide), manufactured by Bristol-Myers Laboratories, in 1985
1463 and 1986, respectively, to treat life-threatening and symptomatic ventricular arrhythmias.¹⁶³ The
1464 drug labeling specifically noted the drugs had not been tested in post-heart-attack patients and
1465 there was no evidence to show either drug improved patient survival.¹⁶⁴ FDA did not approve
1466 either drug for use in patients without symptoms of ventricular arrhythmias.¹⁶⁵

1467

1468 However, immediately after approval many physicians began prescribing antiarrhythmic drugs
1469 such as Tambocor and Enkaid for the unapproved treatment of asymptomatic ventricular
1470 arrhythmias, primarily increased rates of ventricular premature beats in patients who had recently
1471 experienced heart attacks. Asymptomatic ventricular arrhythmias are associated with decreased
1472 survival in such patients.¹⁶⁶ These patients did not exhibit symptoms of ventricular arrhythmias
1473 as indicated on the FDA-approved labeling; rather they had abnormal electrocardiograms
1474 showing ventricular arrhythmias.¹⁶⁷ Many in the medical community hoped that using
1475 Tambocor and Enkaid to reduce asymptomatic ventricular arrhythmias would improve survival
1476 of patients who recently experienced heart attacks.¹⁶⁸

1477

1478 This unapproved use was so widespread that in 1987, the National Institutes of Health (NIH)
1479 launched the Cardiac Arrhythmia Suppression Trial (CAST) to investigate the effectiveness of
1480 antiarrhythmic drugs in post-heart attack patients.¹⁶⁹ NIH intended recruitment for CAST to last
1481 three years but discontinued the study of antiarrhythmic drugs after only two years when
1482 preliminary findings showed the risk of death was 2.5 times greater for patients in the treatment

¹⁶² FDA, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, (Apr. 30, 2009), at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm>.

¹⁶³ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁶⁴ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁶⁵ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁶⁶ Declaration of Rachel E. Sherman, MD, Par Pharm., Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

¹⁶⁷ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁶⁸ Declaration of Rachel E. Sherman, MD, Par Pharm., Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012).

¹⁶⁹ FDA, *Promotion of Unapproved Drugs and Medical Devices: Statement of William B. Schultz*, (1996), at <http://www.fda.gov/newsevents/testimony/ucm115098.htm>. See also News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

1483 versus control group.¹⁷⁰ The trial's Data and Safety Monitoring Board¹⁷¹ also recommended this
1484 arm of the study be halted finding that it was unlikely these drugs could show a benefit in post-
1485 heart attack patients.¹⁷²

1486
1487 Because of the CAST study, 3M Pharmaceuticals and Bristol-Myers notified doctors that
1488 Tambocor and Enkaid should only be prescribed for patients with life-threatening arrhythmias,
1489 and revised the drug labeling to include this warning.¹⁷³ Bristol-Myers announced in September
1490 1991 that it was withdrawing Enkaid from the market given continuing uncertainty regarding the
1491 implications of the CAST study, and the increasing availability of alternative therapies.¹⁷⁴ While
1492 Tambocor remained on the market after publication of the CAST results, FDA required 3M
1493 Pharmaceuticals to add two boxed warnings to the drug label cautioning patients who
1494 experienced a recent heart attack or suffered from chronic atrial fibrillation not to use the drug.¹⁷⁵
1495

¹⁷⁰ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁷¹ See *supra* note 156.

¹⁷² Debra S. Echt et al., *Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial*, 324 NEW ENG. J. MED. 781 (1991).

¹⁷³ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁷⁴ See News Release, Bristol-Myers Squibb Company (Sept. 16, 1991) and FDA Talk Paper, *Update: Antiarrhythmic Drugs* (Mar. 10, 1995), at http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL21.pdf.

¹⁷⁵ See ABRAMS' CLINICAL DRUG THERAPY: RATIONALES FOR NURSING PRACTICE 464 (Geraldyn Frandsen & Sandra Smith Pennington eds., 10th ed. 2014).

1496 **APPENDIX C**

1497 **EXAMPLES OF PRODUCTS MARKETED FOR UNAPPROVED USES THAT CAUSED**
1498 **HARM**

1499 **A. Aranesp (Amgen, Inc.)**

1500 Aranesp, manufactured by Amgen, is one of the ESAs discussed above, approved for treatment
1501 of anemia associated with chronic renal failure and for the treatment of chemotherapy-induced
1502 anemia in patients.
1503

1504
1505 Amgen later sought FDA approval for a third indication for Aranesp – to treat anemia caused by
1506 cancer itself (as opposed to anemia caused by chemotherapy). FDA did not approve Amgen’s
1507 application for this indication as Amgen failed to provide sufficient evidence demonstrating
1508 Aranesp was safe and effective for this indication.¹⁷⁶ Despite not receiving approval, Amgen
1509 began promoting Aranesp to treat anemia caused by cancer, as well as the use of less frequent,
1510 larger doses of the drug (which also had not been approved).¹⁷⁷ Sales representatives promoted
1511 the unapproved use to health care providers with “the very same studies that the FDA had
1512 rejected as insufficient to support the safety and efficacy of those off-label uses, when Amgen
1513 had applied to expand Aranesp’s label to encompass them.”¹⁷⁸
1514

1515
1516 Meanwhile, in January 2007, an Amgen-sponsored trial studying Aranesp showed that Aranesp
1517 increased the number of patient deaths when compared to a placebo group.¹⁷⁹ Other studies
1518 suggested similar results.¹⁸⁰ FDA issued a safety alert in February 2007 warning that Aranesp
1519 was not only ineffective in reducing the need for red blood cell transfusions in anemic cancer
1520 patients not receiving chemotherapy, but that the drug also caused a higher rate of patient deaths

¹⁷⁶ Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays \$762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), at <http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal>.

¹⁷⁷ Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays \$762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), at <http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal>.

¹⁷⁸ Department of Justice, *Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays \$762 Million to Resolve Criminal Liability and False Claims Act Allegations*, (Dec. 19, 2012), at <http://www.justice.gov/opa/pr/amgen-inc-pleads-guilty-federal-charge-brooklyn-ny-pays-762-million-resolve-criminal>.

¹⁷⁹ Sean Harper, M.D., Amgen, *Aranesp (darbepoetin alfa) Dear Healthcare Professional Letter*, (Jan. 26, 2007), at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153899.htm>.

¹⁸⁰ FDA, *Information for Healthcare Professionals: Erythropoiesis Stimulating Agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)]*, (Nov. 8, 2007), at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126481.htm>.

1521 compared to the standard of care.¹⁸¹ In light of these findings, FDA also required Aranesp to
1522 bear a boxed warning to advise the public of these risks.¹⁸²

1523

1524 **B. Seprafilm (Genzyme Corp.)**

1525

1526 In 1996, FDA approved Genzyme Corporation’s Seprafilm.¹⁸³ Seprafilm is a thin film indicated
1527 for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce
1528 the incidence, extent, and severity of postoperative adhesions between the abdominal wall and
1529 the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the
1530 uterus and surrounding structures.¹⁸⁴ A laparotomy is a surgical procedure that involves making
1531 an incision into the abdominal wall that allows the surgeon to gain access to and visualize the
1532 internal organs using standard surgical instruments.¹⁸⁵ By contrast, laparoscopy is a surgical
1533 technique in which short, narrow tubes are inserted into the abdomen through smaller incisions;
1534 Seprafilm has never been FDA-approved for use in laparoscopic surgical procedures.¹⁸⁶

1535

1536 Between 2005 and 2010, in response to diminishing sales due to a diminishing number of
1537 laparotomies being performed, Genzyme sales representatives taught doctors and other staff to
1538 alter Seprafilm into a “slurry” – a new medical device that lacked an approved application for
1539 premarket approval – for use in laparoscopic surgeries by inserting a catheter filled with the
1540 mixture into the body and squirting it into the abdominal cavity.¹⁸⁷ Genzyme also distributed
1541 promotional material that implied Seprafilm had been proven safe and effective for use in
1542 gynecologic cancer surgeries, even though Seprafilm’s labeling cautioned that the device had not
1543 been clinically evaluated in the presence of malignancies.¹⁸⁸

1544

¹⁸¹ See FDA, *Aranesp (darbepoetin alfa) February 2007*, at

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150817.htm>

(last updated Aug. 27, 2013).

¹⁸² See FDA, *Aranesp (darbepoetin alfa) February 2007*, at

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150817.htm>

(last updated Aug. 27, 2013).

¹⁸³ See FDA, *Premarket Approval (PMA) Database: Seprafilm P950034*, at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P950034> (last visited Dec. 23, 2016).

¹⁸⁴ See FDA, *Premarket Approval of Genzyme Corporation’s Seprafilm Bioresorbable Membrane – ACTION*, (Aug. 12, 1996), at http://www.accessdata.fda.gov/cdrh_docs/pdf/p950034.pdf (last visited Dec. 23, 2016).

¹⁸⁵ Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at <https://www.justice.gov/opa/file/767301/download> (last visited Dec. 23, 2016).

¹⁸⁶ Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at <https://www.justice.gov/opa/file/767301/download> (last visited Dec. 23, 2016).

¹⁸⁷ See Department of Justice, *Genzyme Corp. to Pay \$22.28 Million to Resolve False Claims Allegations Related to “Slurry” Used in Patients*, (Dec. 20, 2013), at <https://www.justice.gov/opa/pr/genzyme-corp-pay-2228-million-resolve-false-claims-allegations-related-slurry-used-patients>; *Deferred Prosecution Agreement*, United States v.

Genzyme Corp., No 8:15-cr-00352-JSM-AEP-1, (M.D. Fla. Aug. 31, 2015), at <https://www.justice.gov/opa/file/767286/download>.

¹⁸⁸ See Department of Justice, *Genzyme Corporation to Pay \$32.5 Million to Resolve Criminal Liability Relating to Seprafilm*, (Sept. 3, 2015), at <https://www.justice.gov/opa/pr/genzyme-corporation-pay-325-million-resolve-criminal-liability-relating-seprafilm>; *Deferred Prosecution Agreement*, United States v. Genzyme Corp., No 8:15-cr-00352-JSM-AEP-1, (M.D. Fla. Aug. 31, 2015), at <https://www.justice.gov/opa/file/767286/download>; Department of Justice, *Information*, United States v. Genzyme Corp., No 8:15-cr-352-JSM-AEP, (M.D. Fla. Sept. 3, 2015), at <https://www.justice.gov/opa/file/767301/download> (last visited Dec. 23, 2016).

1545 **C. Depakote (Abbott Laboratories)**

1546
1547 In 1983, FDA approved Abbott Laboratories' drug Depakote to treat patients suffering from
1548 epileptic seizures.¹⁸⁹ Subsequently, in 1996, FDA approved Depakote to treat bipolar mania and
1549 for prevention of migraines.¹⁹⁰ Abbott sponsored a study of Depakote for treatment of agitation
1550 in elderly patients with dementia, but that trial was discontinued in 1999 after subjects
1551 experienced an increase in drowsiness, dehydration, and anorexia.¹⁹¹ Abbott also sponsored two
1552 trials to study Depakote for treatment of schizophrenia, but both failed to show patients benefited
1553 from Depakote when compared to a control group. Abbott waited nearly two years to share
1554 these study results with its sales representatives and approximately four years to publish the
1555 results.¹⁹²

1556
1557 Despite these study results, from 1998 through 2006, Abbott sales staff reportedly targeted
1558 nursing home employees to promote unapproved uses of Depakote, including for treatment of
1559 agitation and aggression in elderly patients suffering from dementia.¹⁹³ According to
1560 Department of Justice allegations, the company also marketed Depakote for treatment of
1561 schizophrenia in nursing homes from 2001 until 2006.¹⁹⁴

1562
1563 **D. Neurontin (Warner-Lambert)**

1564
1565 In 1993, FDA approved Warner-Lambert's drug Neurontin as an adjunctive or supplemental
1566 medication to control partial onset seizures in adults.¹⁹⁵ In 1996, Warner-Lambert sought FDA
1567 approval to use Neurontin as the sole drug (monotherapy) for epileptic seizures, and sought an
1568 increase in Neurontin's effective dose range and maximum recommended dose. FDA did not
1569 approve the indication, stating that Warner-Lambert did not provide sufficient evidence to
1570 support approval of Neurontin as a monotherapy,"¹⁹⁶ and FDA would not approve the changes in

¹⁸⁹ In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012).

¹⁹⁰ In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012). *See also* FDA, *Drugs@FDA.gov: FDA Approved Drug Products Depakote (divalproex sodium) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=018723> (last visited Dec. 21, 2016).

¹⁹¹ In re Abbott Depakote S'holder Derivative Litig., 909 F. Supp. 2d 984, 989 (N.D. Ill. 2012); *see also* Department of Justice, *Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), at <http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote>.

¹⁹² Department of Justice, *Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), at <http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote>.

¹⁹³ Department of Justice, *Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), at <http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote>.

¹⁹⁴ Department of Justice, *Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigation of Off-Label Promotion of Depakote*, (May 7, 2012), at <http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote>.

¹⁹⁵ Alicia Mack, *Examination of the Evidence for Off-Label Use of Gabapentin*, 9 J MANAGED CARE PHARM. 559 (2003).

¹⁹⁶ David Kessler Expert Report, In re Neurontin Mktg., Sales Practices and Prod. Liab. Litig., available at 2008 WL 7018942 (D. Mass. July 31, 2008).

1571 dose because controlled trials failed to provide evidence that higher doses of Neurontin are more
1572 effective than those recommended.¹⁹⁷ In 1996, the firm sought FDA approval of Neurontin as a
1573 monotherapy for partial seizures in adult patients not previously treated with an antiepileptic
1574 drug. However, in 1997, FDA declined to approve the additional use because Warner-Lambert
1575 again failed to provide evidence showing Neurontin was a safe and effective monotherapy for
1576 partial seizures, as required to support FDA approval of a new indication.¹⁹⁸

1577
1578 Despite FDA’s decision, Warner-Lambert marketed Neurontin as monotherapy to treat epileptic
1579 seizures and a wide array of other ailments – including broad neuropathic pain, migraine
1580 headache, and bipolar disorder – all of which were unapproved uses of the drug.¹⁹⁹ This
1581 marketing occurred despite there being no scientific evidence supporting use of Neurontin to
1582 treat many of these diseases or conditions. For example, Warner-Lambert promoted Neurontin
1583 as an effective treatment for bipolar disorder, even though a scientific study conducted between
1584 1996 and 1997 demonstrated that a placebo worked as well or better than the drug.²⁰⁰
1585 Warner-Lambert itself estimated that “only about ten percent of Neurontin prescriptions that year
1586 were for the FDA-approved on-label uses for epilepsy or postherpetic neuralgia, and that more
1587 than a third of prescriptions were for unapproved treatment of neuropathic pain, migraine or
1588 headache, or bipolar disorder.”²⁰¹

1589 **E. Atypical Antipsychotics**

1590
1591
1592 Antipsychotic drugs are one of the top selling classes of pharmaceuticals. In 2008, sales of
1593 antipsychotic drugs exceeded \$10 billion in retail U.S. pharmacies, representing the largest
1594 expenditure for any single drug class.²⁰² FDA generally approves these drugs for narrow
1595 indications, such as treatment of schizophrenia or bipolar disorder in adults. However, despite
1596 FDA approving these drugs to treat disorders that affect a small minority of the U.S. population,
1597 drug manufacturers have marketed antipsychotic drugs for unapproved uses, with serious public
1598 health risks and consequences, as the examples below illustrate.

1599

¹⁹⁷ In re Neurontin Mktg. & Sales Practices Litig., No. 04-CV-10739-PBS, 2011 WL 3852254, at *6 (D. Mass. Aug. 31, 2011), aff’d, 712 F.3d 21 (1st Cir. 2013).

¹⁹⁸ David Kessler Expert Report, In re Neurontin Mktg., Sales Practices and Prod. Liab. Litig., available at 2008 WL 7018942 (D. Mass. July 31, 2008).

¹⁹⁹ In re Neurontin Mktg. & Sales Practices Litig., No. 04-CV-10739-PBS, 2011 WL 3852254, at *1 (D. Mass. Aug. 31, 2011).

²⁰⁰ In re Neurontin Mktg. & Sales Practices Litig., No. 04-CV-10739-PBS, 2011 WL 3852254, at *12 (D. Mass. Aug. 31, 2011) aff’d, 712 F.3d 21 (1st Cir. 2013).

²⁰¹ In re Neurontin Mktg. & Sales Practices Litig., 712 F.3d 21, 28 (1st Cir.), cert. denied sub nom., Pfizer Inc. v. Kaiser Found. Health Plan, Inc., 187 L. Ed. 2d 594 (2013).

²⁰² Rosanne Spector, *Evidence lacking for widespread use of costly antipsychotic drugs, says researcher*, (Jan. 6, 2011), at <http://med.stanford.edu/news/all-news/2011/01/evidence-lacking-for-widespread-use-of-costly-antipsychotic-drugs-says-researcher.html>.

1600 **1. Zyprexa (Eli Lilly)**

1601
1602 FDA approved Zyprexa, manufactured by Eli Lilly, in 1996 for treatment of schizophrenia.²⁰³ In
1603 2000, FDA also approved Zyprexa for the treatment of bipolar disorder.²⁰⁴

1604
1605 In 1999, Eli Lilly began promoting Zyprexa for a number of unapproved uses in nursing homes
1606 and assisted living facilities.²⁰⁵ Eli Lilly marketed Zyprexa for treatment of agitation,
1607 aggression, hostility, dementia, Alzheimer’s dementia, depression, and generalized sleep disorder
1608 in elderly patients.²⁰⁶ In 2000, Eli Lilly began promoting Zyprexa to primary care physicians –
1609 even though these physicians do not typically treat schizophrenia or bipolar disorder.²⁰⁷ Eli Lilly
1610 trained sales staff to promote Zyprexa to primary care physicians for the unapproved treatment of
1611 anxiety, irritability, depression, nausea, Alzheimer’s disease, and other mood disorders.²⁰⁸

1612
1613 Around this time, FDA received clinical trial information showing elderly patients taking
1614 Zyprexa had in increased risk of death due to cardiovascular and infectious diseases. In addition,
1615 these trials showed Zyprexa had little or no benefit in reducing dementia-related symptoms and
1616 caused weight gain, increased cholesterol levels, and diabetes. Studies found that unapproved
1617 use of Zyprexa was responsible for widespread adverse effects and many deaths.²⁰⁹

1618
1619 In 2005, FDA issued a public health advisory warning that use of antipsychotic medications,
1620 such as Zyprexa, was associated with increased mortality in elderly patients. FDA also required
1621 a boxed warning be added to Zyprexa stating that “[e]lderly patients with dementia-related
1622 psychosis treated with atypical antipsychotic drugs are at increased risk of death compared to
1623 placebo.”²¹⁰

²⁰³ FDA, *Drugs@FDA.gov: FDA Approved Drug Products Zyprexa (olanzapine) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020592> (last visited Dec. 20, 2016).

²⁰⁴ FDA, *Drugs@FDA.gov: FDA Approved Drug Products Zyprexa (olanzapine) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020592> (last visited Dec. 20, 2016).

²⁰⁵ Department of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), at <http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html>.

²⁰⁶ Department of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), at <http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html>.

²⁰⁷ Department of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), at <http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html>.

²⁰⁸ Department of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (Jan. 15, 2009), at <http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html>.

²⁰⁹ FDA, *Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*, (Apr. 11, 2005), at <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171>.

²¹⁰ FDA, *Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*, (Apr. 11, 2005), at <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171>.

1625 **2. Geodon (Pfizer)**

1626
1627 In 2001, FDA approved Geodon, manufactured by Pfizer, for treatment of schizophrenia.²¹¹
1628 However, Pfizer promoted Geodon for treatment of many conditions not approved by FDA,
1629 including treatment of depression, mood disorder, anxiety, aggression, dementia, attention deficit
1630 hyperactivity disorder, obsessive-compulsive disorder, autism, and post-traumatic stress disorder,
1631 in both children and adults.²¹² Pfizer hired physicians across the U.S. to help promote
1632 unapproved Geodon use in children by giving promotional lectures encouraging doctors to
1633 prescribe the drug to children, despite the fact that Geodon was not approved for use in children,
1634 and to prescribe the drug at substantially higher amounts than the approved dosages.²¹³
1635

1636 **3. Seroquel (AstraZeneca)**

1637
1638 FDA approved Seroquel, manufactured by AstraZeneca, to treat symptoms of psychotic
1639 disorders, for short-term treatment of bipolar mania, and for treatment of bipolar depression.²¹⁴
1640 Between 2001 and 2006, AstraZeneca widely promoted Seroquel to psychiatrists and other
1641 health care providers for unapproved uses. AstraZeneca marketed Seroquel for treatment of
1642 aggression, Alzheimer's disease, anger management, anxiety, attention deficit disorder, bipolar
1643 maintenance, dementia, depression, mood disorder, post-traumatic stress disorder, and
1644 sleeplessness, despite the fact FDA has not found Seroquel to be safe and effective for these
1645 indications. AstraZeneca marketed Seroquel to doctors who do not typically treat schizophrenia
1646 or bipolar disorder, including doctors who treat the elderly, primary care physicians, pediatric
1647 and adolescent physicians, and to doctors working in long-term care facilities and prisons. The
1648 company promoted unapproved uses of Seroquel through company-sponsored continuing
1649 medical education programs and recruited doctors to serve as authors of articles that were
1650 ghostwritten by medical literature companies and about studies the doctors in question did not
1651 conduct.²¹⁵
1652

1653 **4. Abilify (Bristol-Myers Squibb)**

1654
1655 In 2002, FDA approved Abilify, manufactured by Bristol-Myers Squibb Company (BMS), for
1656 treatment of schizophrenia. Abilify was subsequently approved for other indications. However,
1657 BMS promoted Abilify for treatment of conditions not approved by FDA, including use in
1658 elderly patients with symptoms consistent with dementia as well as for unapproved uses in

²¹¹ FDA, *Drugs@FDA.gov: FDA Approved Drug Products Geodon (ziprasidone hydrochloride) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020825> (last visited Dec. 20, 2016).

²¹² Department of Justice, *Pharmaceutical Company Pfizer, Inc. to Pay \$301 Million for Off-Label Drug Marketing*, (Sept. 2, 2009), at <http://www.justice.gov/archive/usao/pae/News/2009/sep/pfizerrelease.pdf>.

²¹³ Department of Justice, *Pharmaceutical Company Pfizer, Inc. to Pay \$301 Million for Off-Label Drug Marketing*, (Sept. 2, 2009), at <http://www.justice.gov/archive/usao/pae/News/2009/sep/pfizerrelease.pdf>.

²¹⁴ FDA, *Drugs@FDA.gov: FDA Approved Drug Products Seroquel (quetiapine fumarate) NDA*, at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020639> (last visited Dec. 20, 2016).

²¹⁵ Department of Justice, *Pharmaceutical Giant AstraZeneca to Pay \$520 Million for Off-label Drug Marketing*, (Apr. 27, 2010), at <http://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing>.

1659 children.²¹⁶ In 2006, Abilify received a boxed warning against its use in the treatment of
1660 dementia-related psychosis. The warning states: “Elderly patients with dementia-related
1661 psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not
1662 approved for the treatment of patients with dementia-related psychosis.”²¹⁷

1663 **F. Metacam (Boehringer Ingelheim Vetmedica, Inc.)**

1664
1665
1666 In 2003, FDA approved the use of Metacam (meloxicam) oral tablets as a non-steroidal anti-
1667 inflammatory drug (NSAID) for the control of pain and inflammation associated with
1668 osteoarthritis in dogs.²¹⁸ The following year, FDA approved Metacam for use as a subcutaneous
1669 injection in both cats and dogs.²¹⁹ Although cats are particularly sensitive to NSAIDs due to a
1670 limited ability to break them down compared to other species,²²⁰ at that time there were no
1671 NSAIDs available to treat pain and inflammation in cats. FDA therefore balanced the risks
1672 against the benefits and approved Metacam for cats only as a single-dose, one-time injection
1673 prior to surgery for the control of postoperative pain and inflammation associated with
1674 orthopedic surgery, ovariohysterectomy, and castration.²²¹

1675
1676 In a tolerance study submitted to FDA in 2004 to support approval of Metacam, Boehringer
1677 Ingelheim Vetmedica, Inc., the manufacturer, found serious risks regarding long-term oral
1678 Metacam use in cats. The purpose of the study was to assess the tolerance in cats following
1679 multiple doses of Metacam over a period of 10 days. The study concluded that Metacam, “when
1680 initially dosed as a subcutaneous injection followed by oral dosing for nine days at [≥ 0.14 mg
1681 per pound] was associated with severe adverse effects, including death.”²²²

1682

²¹⁶ Delaware State Government Press Release, *Forty-Three Attorneys General Reach Consumer Protection Settlement With Bristol-Myers Squibb Company Over Abilify Marketing* (Dec. 8, 2016), at <http://news.delaware.gov/2016/12/08/a1/>; Department of Justice, *Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing* (Sept. 28, 2007), at https://www.justice.gov/archive/opa/pr/2007/September/07_civ_782.html.

²¹⁷ Abilify Prescribing Information (last revised Aug. 2016), at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021436s041.021713s032.021729s024.021866s0261bl.pdf.

²¹⁸ FDA, *Freedom of Information Summary, NADA 141-213 Metacam*, (Apr. 15, 2003), at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118006.pdf>.

²¹⁹ FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf>.

²²⁰ FDA, *Over-the-Counter Pain Relievers for People—Are They Safe for Pets?*, at <http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm392732.htm#OTC> (last updated Oct. 26, 2016).

²²¹ See FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf>; FDA, *NADA Number: 141-219*, at <http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=141-219> (last visited Dec. 21, 2016).

²²² FDA, *Freedom of Information Summary, NADA 141-219 Metacam*, (Oct. 28, 2004), at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm118027.pdf>.

1683 After Metacam was approved on a limited basis for use in cats, the manufacturer then began
1684 promoting Metacam for unapproved uses. In an April 2005 Notice of Violation letter, FDA cited
1685 a free CD that the manufacturer was distributing to veterinarians titled “Pain: How to
1686 Understand, Recognize, Treat, Stop.”²²³ The CD mailer included the photographic images of a
1687 parrot, guinea pig, cat, reptile, and dog, suggesting that Metacam was safe and effective for uses
1688 that had never been demonstrated.

1689
1690 By September 2010, FDA had received hundreds of adverse event reports associated with oral
1691 dosing of Metacam, including reports of several feline deaths, including from euthanization, and
1692 numerous reports of kidney failure.²²⁴ Based on these reports, FDA asked the manufacturer to
1693 add a boxed warning to Metacam explicitly stating that “[r]epeated use of meloxicam in cats has
1694 been associated with acute renal failure and death. Do not administer additional injectable or
1695 oral meloxicam to cats.”²²⁵

²²³ FDA, *Notice of Violation letter to Boehringer Ingelheim Vetmedica, Inc.*, (Apr. 19, 2005), at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/ucm042460.pdf>.

²²⁴ FDA, *CVM ADE Comprehensive Clinical Detail Report Listing*, (Jan. 1, 1987-Apr. 30, 2013), at <http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM055409.pdf> (last visited Dec. 20, 2016).

²²⁵ See FDA, *Information about the Boxed Warning on METACAM® (meloxicam) Labels*, at <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm472976.htm> (last updated Nov. 17, 2015).