



April 19, 2017

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on “Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products” [Docket No. FDA-2016-N-1149]

Dear Sir or Madam:

The Pew Charitable Trusts (Pew) offers these comments regarding the Food and Drug Administration’s (FDA) proposal to engage in a comprehensive review of its regulations and policies governing firms’ communications about unapproved (“off-label”) uses of approved medical products. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on the quality and safety of drugs and medical devices.

We appreciate the opportunity to offer public comment on FDA’s review of off-label communications of approved medical products. FDA plays a critical role in ensuring public health and safety by reducing the harms associated with medical products for uses that may not be safe and effective. FDA looks to a firm’s communications about its products to help determine their intended use, and may take action against a sponsor that does not receive FDA approval for any use that it is promoting. However, medical products are frequently used in populations or for purposes that are different from those considered in the FDA-approved label, and drug and device sponsors continue to collect and monitor information about such off-label uses of their products that are on the market. Their role in using such information to promote products has been the subject of debate – some contend that patients would be well served if manufacturers had greater latitude to inform providers about truthful and non-misleading information from the published medical literature. Others are concerned that off-label communication may lead providers to make decisions based on inadequate information. FDA is widely recognized as the gold standard for reviewing evidence of safety and effectiveness. As FDA reexamines its policies related to firms’ communications regarding unapproved uses of approved medical products, the agency must consider the interests of public health, medical innovation, and constitutional law.

Substantiation for Promotional Claims

The Federal Food Drug and Cosmetic Act (FDCA) and the Public Health Service Act (PHS) authorize FDA to regulate the introduction of medical products into interstate commerce. Under these authorities (hereafter referred to as “FDA Authorities”), FDA can prohibit the sale of a product that does not meet the requirements for approval, or is otherwise misbranded or adulterated.

During pre-market review, firms must establish safety and efficacy of the medical product for each intended use, typically by providing FDA with evidence from clinical trials.¹ FDA considers the risks and

¹ The precise standards and evidentiary requirements for establishing safety and effectiveness vary based on the type and risk of the product. Most drugs, for example, are approved only once the sponsor has provided “substantial evidence” consisting of “adequate and well-controlled investigations,” Federal Food Drug and Cosmetic Act of 1938

benefits of a product for its intended use and determines whether the product is approved or cleared for introduction into interstate commerce as a result of having satisfied the pre-market review requirements. If a product initially approved/cleared for one use is later determined to be beneficial for another use, the product sponsor can submit a supplemental application supporting the new use. This process is important because the risk-benefit profile for a product may change if it is used under different conditions or in a new population.

The law requires that any medical product marketed to U.S. consumers bear “adequate directions for use,”² so that providers and their patients understand the benefits and risks of the drug, and how to use it safely. A drug or device that is not accompanied by “adequate directions” for its intended use is misbranded, and the firm marketing it may be subject to criminal penalties.³ To determine the “intended use” of a drug or device, FDA looks to “objective intent of the persons legally responsible for the labeling of drugs [and devices]” as evidenced by, among other factors, “oral or written statements by such persons or their representatives.”⁴ The intended use may include any purposes for which the product is “offered and used,” even if it is not labeled or advertised for that purpose; thus, the manufacturer can change the intended use of the product after it is on the market through its communications about that product.⁵

While promotional speech can be evidence of intended use, the Supreme Court has recognized pharmaceutical marketing as “a form of expression protected by the *Free Speech Clause of the First Amendment*.”⁶ Thus, when the government sought to prosecute a pharmaceutical sales representative for off-label claims in *U.S. v. Caronia*, the U.S. Court of Appeals for the Second Circuit overturned his conviction, ruling that the government cannot prosecute firm representatives simply for making off-label promotion statements.⁷

However, even *Caronia* acknowledged that promotion of off-label uses may be used as evidence in determining whether a drug is misbranded, and thus illegal, under the FDCA.⁸ Speech can be used as

(FDCA 505(b)), which usually, but not always, requires two randomized and controlled clinical trials. 21 C.F.R. §314.126(b); *but see* 21 U.S.C. 355(d) (providing an exception to the two-trial rule). Devices are divided into three categories: 1) the lowest-risk “class I” devices are typically exempt from premarket notification; 2) medium risk “Class II” devices require pre-market notification and are “cleared” for marketing if FDA concludes that evidence demonstrates that the device is substantially equivalent to a predicate device that is already legally on the market; and 3) the highest-risk “Class III” devices require pre-market approval, which requires “valid scientific evidence,” including clinical data, that provide a reasonable assurance of safety and effectiveness. Federal Food, Drug and Cosmetic Act of 1938 (FDCA 513(a)(1)). Importantly, the classification of a device depends in part upon its intended use, so a device marketed for one use may be cleared as a Class II device, but if the same device is intended for a different use from the predicate device, it may require FDA approval. Federal Food Drug and Cosmetic Act of 1938 (FDCA 513(i)).

² Food Drug and Cosmetic Act of 1938, Pub. L. No. 75-717, Sec. 502(f), 52 Stat. 1040 (1938).

³ Food Drug and Cosmetic Act of 1938, Pub. L. No. 75-717, Sec. 303(a)(2), 52 Stat 1040 (1938).

⁴ 21 C.F.R. §201.128 (drugs); 21 C.F.R §801.4 (devices).

⁵ *Id.*

⁶ *Sorrell vs. IMS Health, Inc.* 564 U.S. 552, 557 (2011).

⁷ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). While some in the academic community have argued that *Caronia* was wrongly decided, we have not addressed that possibility because the narrow scope of its holding leaves room for FDA to continue to require substantiation for each intended use. *See e.g.* Christopher Robertson and Aaron S. Kesselheim, *Regulating Off-Label Promotion: A Critical Test*, *N Engl J Med* (2016); 375:2313-2315, <http://www.nejm.org/doi/full/10.1056/NEJMp1611755#t=article>.

⁸ *Caronia*, 703 F.3d at 162; *see also* *Polansky v. Pfizer*, 822 F.3d 613, 615 n.2 (2d Cir. 2016) (“*Caronia* left open the government’s ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug’s FDA-approved label.”); *Shuker v. Smith and Nephew*, 2016 U.S.

evidence “to establish the elements of a crime, or to prove motive or intent.”⁹ Thus, while FDA cannot prohibit firms from promoting uses of products that have not been approved, it can use promotional statements as evidence of the manufacturer’s intended use for the product, and prosecute the firm if it has not received FDA approval for labeling that would provide “adequate directions” for each intended use.^{10,11} While truthful and non-misleading promotional statements about off-label uses cannot be a considered a criminal act in and of itself, it can be used as evidence to determine the illegal act of misbranding.

To be meaningful, those adequate directions for use must be supported by clinical evidence in the population for whom the drug is intended. This information is important for weighing the benefits and risks of a treatment and deciding under what circumstances it should be recommended. As will be detailed below, even fair and unbiased representations of data that fall short of meeting FDA’s approval standard may misdirect providers and patients regarding the benefits and risks of medical products. FDA has a responsibility to ensure the safety and effectiveness of medical products sold to U.S. consumers, and part of fulfilling that responsibility is ensuring that products offered for sale are accompanied by labeling that provides adequate directions for the product’s use.¹²

Off-Label Use of Medical Products

Medical products are frequently used off-label. Such use is legal and an important part of the toolkit for physicians as they encounter clinical situations that may not mimic those in clinical trials. For example, off-label uses may be a necessity when limited treatment options exist. Off-label use of medical products occurs when a healthcare provider prescribes a product for an indication (e.g., a disease or symptom) that has not been approved by FDA. The term “off-label” may also apply to, for example, using a medication in a patient population, dosage, or dosage form that has not received FDA approval.¹³ Studies from the

Dist. LEXIS 134584, 21-22 (E.D. Pa. 2016) (citing *Caronia*’s intended use theory in the context of a device misbranding claim).

⁹ *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993).

¹⁰ In *Pom Wonderful, LLC v. FTC*, the D.C. Circuit upheld the Federal Trade Commission’s order determining that a beverage manufacturer’s health claims about its product were misleading because they were not adequately substantiated. 414 U.S. App. D.C. 111, 777 F.3d 478 (2015). Although the Court took issue with the specific nature of FTC’s substantiation requirement in that instance, it acknowledged that it did not offend the Constitution for the agency to require substantiation before the firm could make promotional claims. *Id.* at 502-03. This case underscores that the First Amendment does not protect claims made in the absence of supporting evidence.

¹¹ One notable 2015 district court case cited *Caronia* in holding that FDA could not prohibit a drug sponsor from making promotional statements that were truthful and non-misleading. *Amarin Pharma Inc. v. U.S. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015). In *Amarin*, however, the sponsor sought to make claims about the prescription form of a drug that FDA had already determined were permissible for non-prescription formulations of the same active ingredient. In this way, the *Amarin* case is unique because FDA had already determined that the claims were substantiated. In most off-label promotion cases, FDA has not been presented evidence to support the intended use established by the off-label claim.

¹² See *Thompson v. Western States Medical Center*, 535 U.S. 357, 369 (2002). (“[T]he safety and effectiveness of a new drug needs to be established by rigorous, scientifically valid clinical studies because impressions of individual doctors, who cannot themselves compile sufficient safety data, cannot be relied upon [T]he Government has every reason to want as many drugs as possible to be subject to [the] approval process.”).

¹³ U.S. Food and Drug Administration, “Draft Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers,” January 2017, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf>, accessed April 7, 2017; Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, “Ten Common Questions (and Their Answers) About Off-label Drug Use,” *Mayo Clinic Proceedings* 87, no. 10 (2012): 982-990, doi: 10.1016/j.mayocp.2012.04.017.

U.S. and Canada estimate that between 11 and 21 percent of medications are prescribed for an off-label indication,¹⁴ and some studies suggest that off-label prescribing may be more prevalent among certain subpopulations, such as children.¹⁵ Off-label use of antidepressants, anticonvulsants, and antipsychotic medications are most common.¹⁶ One study found that two of the top-selling drugs in 2009, which had initially been approved as orphan drugs, were used mostly for off-label indications.¹⁷

It is important to note that the FDA has already provided a legal framework to allow “safe harbors” under which firms can distribute scientific and medical publications on unapproved new uses of approved products to healthcare providers or sophisticated audiences (e.g., payors) through scientific exchange of information. Communications about unapproved uses of approved medications can support healthcare decision-making by providing physicians with additional information about a treatment’s use beyond that which is listed on the label. In the circumstances of scientific exchange, where manufacturer communication about a product does not establish an intent to offer the product for sale for a new intended use, FDA does not view the communication as evidence of a violation of the FDCA, even if the communication is about an off-label use.¹⁸

Some stakeholders suggest that FDA should provide more clear guidance permitting certain communications of off-label uses of medical products.¹⁹ Manufacturer participation in scientific exchange regarding marketed products may be beneficial, particularly with respect to audiences, such as payors, that have both the capacity and incentive to examine the data and methodology to support informed decision-making. However, when firms engage in communication about off-label uses that goes beyond scientific exchange and involves the promotion of products for off-label uses, those uses should be supported by sufficient evidence of safety and efficacy. The government has an important role in ensuring public health and safety by reducing the harms associated with the off-label promotion of products for uses that have not been demonstrated to be safe or effective.

Public Health Implications of Off-Label Communication

¹⁴ Tewodros Eguale, et al. “Drug, Patient, and Physician Characteristics Associated With Off-label Prescribing in Primary Care,” *Archives of Internal Medicine* 172, no. 10 (2012): 781-788, doi: 10.1001/archinternmed.2012.340 and David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, “Off-label Prescribing Among Office-Based Physicians,” *Archives of Internal Medicine* 166, no 9: 1021-1026, doi:10.1001/archinte.166.9.1021.

¹⁵ Samir S. Shah, et al. “Off-label Drug Use in Hospitalized Children,” *Archives of Pediatric and Adolescent Medicine* 161, no. 3 (2007): 282-290, doi:10.1001/archpedi.161.3.282.

¹⁶ Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, “Ten Common Questions (and Their Answers) About Off-Label Drug Use,” *Mayo Clinic Proceedings* 87, no. 10 (2012): 982-990, doi: 10.1016/j.mayocp.2012.04.017.

¹⁷ Aaron S. Kesselheim et al., “The Prevalence and Cost of Unapproved Uses of Top-Selling Orphan Drugs,” *Public Library of Science One* 7, no. 2 (2012): e31894, doi: 10.1371/journal.pone.0031894.

¹⁸ U.S. Food and Drug Administration, *Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices*, February 2014, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf>, accessed February 13, 2017; U.S. Food and Drug Administration, *Guidance for Industry and Review Staff, Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers*, January 2017, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537347.pdf>; and U.S. Food and Drug Administration, *Guidance for Industry, Medical Product Communications That are Consistent With the FDA-Required Labeling – Questions and Answers*, January 2017, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537130.pdf>.

¹⁹ See e.g., U.S. Food and Drug Administration, Public Meeting: Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, November 9, 2016 (statement of Michael Labson, Covington & Burling, LLP, on behalf of Pharmaceutical Research and Manufacturers of America (PhRMA)).

Congress has determined that before manufacturers may market certain medical products to the public, they must establish safety and efficacy, and ensure that labeling is adequate, for each of the products' intended uses. FDA's premarket review requirement exists because Congress made a determination, in response to several historical public health tragedies, that independent scientific review is necessary to assure healthcare providers that products are safe and effective for their intended uses. As is described in more detail below, FDA's independent review of safety and efficacy of medical products for each of their intended uses has prevented harms, inspired the development of robust evidence, and helped stakeholders meaningfully interpret those data. The ability of FDA to protect the public health through its function as an independent scientific authority could be compromised if the agency could not restrict firms from promoting products for sale for uses that have not undergone FDA review.

1. Patients have been harmed by off-label uses of approved medical products

After the initial approval/clearance decision, there can be substantial public health consequences of uses that have not been evaluated through the premarket review process.

For example, FDA approved Cephalon, Inc.'s anti-epilepsy drug Gabitril (tiagabine) in 1997 for use in conjunction with other medications for the treatment of partial seizures in adolescents and adults. From 2001 to 2005, Cephalon promoted Gabitril for treating anxiety, insomnia, and pain — unapproved uses for which there was little clinical data to support the drug's safety and efficacy profile.²⁰ As a result of off-label use, 31 case reports of new-onset seizures were reported.²¹ In 2005, FDA announced the addition of a bolded warning to the labeling of Gabitril to warn prescribers of the risk of seizures in patients without epilepsy being treated with the drug.²² In 2008, Cephalon entered a criminal plea and agreed to pay \$425 million to resolve claims that it marketed Gabitril and two other drugs (Actiq and Provigil) without adequate directions for use in FDA-approved labeling.²³

More recently, GlaxoSmithKline (GSK) plead guilty for failing to report safety data and unlawfully marketing several of its drugs for unapproved uses. One, paroxetine (Paxil), was promoted off-label for treating depression in children under age 18, even though studies had failed to show efficacy in a pediatric population.²⁴ Studies showed that children and adolescents with depression and anxiety disorders taking antidepressants like paroxetine had an increased risk of suicidal thinking and behavior, compared to patients who received a placebo.²⁵ In 2004, FDA required that a black-box warning be added to the labels

²⁰ "September 28, 2008: Pharmaceutical Company Cephalon to Pay \$425 Million for Off-label Drug Marketing," U.S. Food and Drug Administration, Office of Criminal Investigation, accessed March 3, 2017, <https://www.fda.gov/ICECI/CriminalInvestigations/ucm260715.htm>.

²¹ Charlene M. Flowers, Judith A. Racoosin, and Cindy Kortepeter, "Seizure Activity and Off-Label Use of Tiagabine," *The New England Journal of Medicine* 354, no. 7 (2006): 773-774, doi: 10.1056/NEJMc055301.

²² "FDA Public Health Advisory: Seizures in Patients Without Epilepsy Being Treated With Gabitril (tiagabine), February 18, 2005," U.S. Food and Drug Administration, accessed Jan. 11, 2017, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051764.htm>.

²³ *United States v. Cephalon, Inc.*, Crim. No. 08-598, (E.D. Pa.).

²⁴ Wayne Kondro and Barb Sibbald, "Drug Company Experts Advised Staff to Withhold Data about SSRI Use in Children," *Canadian Medical Association Journal* 170, no. 5 (2004): 783, doi:10.1503/cmaj.1040213.

²⁵ U.S. Food and Drug Administration, "Labeling Change Request Letter for Antidepressant Medications," updated April 13, 2016, <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm>, accessed March 23, 2017.

of antidepressants, including paroxetine, indicating the serious safety issues for children and adolescents, and, in 2012, GSK agreed to plead guilty for misbranding the drug.²⁶

Even widespread acceptance of an unapproved use does not guarantee that a medical product is safe or effective for that use. In a descriptive study, researchers in Canada observed that nearly one-third of prescriptions written for antidepressants were for an unapproved use. Of those, only 1 in 6 prescriptions had strong scientific evidence to support the off-label indication.²⁷ While some unsupported uses may be appropriate for discussion in a scientific exchange, firms promoting unsupported off-label use can lead to patient harm. For instance, FDA approved Wyeth Pharmaceutical Inc.'s drugs, Premarin in 1942 and Prempro in 1995, to treat menopausal symptoms. Doctors began prescribing the drugs widely for primary prevention of heart disease in the 1990s based on epidemiological data that suggested a possible cardiovascular benefit, even though FDA had not approved any estrogen products for this use and no manufacturer had provided evidence that the products were safe and effective for the prevention of heart disease.²⁸ FDA determined that the observational data was not strong enough to support a causal association and concluded, "The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself."²⁹ When this use was studied in 1997 as part of the Women's Health Initiative — a large government-sponsored randomized placebo-controlled trial — researchers found an increased risk of stroke and blood clotting associated with Premarin³⁰ and an increased risk of coronary events and breast cancer associated with Prempro.³¹ In January 2003, FDA and Wyeth revised the labeling of Premarin and Prempro to include a boxed warning that the products should not be used for the prevention of heart disease.³²

Lack of adequate evidence can lead to patient harm when the risks of the drug outweigh the benefits. One recent study that systematically evaluated the association between off-label uses of drugs and the risk of adverse drug events among more than 45,000 patients in Canada found that the risk of adverse events was

²⁶ U.S. Department of Justice, "GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data," accessed March 17, 2017, <https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report>.

²⁷ Jenna Wong, et al., "Off-label Indications for Antidepressants in Primary Care: Descriptive Study of Prescriptions From an Indication Based Electronic Prescribing System," *British Medical Journal* 356 (2017): j603, doi:10.1136/bmj.j603.

²⁸ Declaration of Rachel E. Sherman, MD, Par Pharmaceutical, Inc. v. United States, 1:11-cv-1820 (D.D.C. Jan. 11, 2012) and U.S. Food and Drug Administration, "FDA Statement on the Results of the Women's Health Initiative," accessed March 31, 2017, <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135331.htm>.

²⁹ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Approved Labeling, Application Number 21-417, Premarin (Conjugated Estrogen Tablets)," accessed April 7, 2017, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-417_Premarin_prntlbl.pdf.

³⁰ National Institutes of Health, "WHI Study Finds No Heart Disease Benefit, Increased Stroke Risk With Estrogen Alone," accessed February 8, 2017, <https://www.nhlbi.nih.gov/news/press-releases/2004/whi-study-finds-no-heart-disease-benefit-increased-stroke-risk-with-estrogen-alone>.

³¹ 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," *Journal of the American Medical Association* 288 no. 3 (2002): 321-33, doi:10.1001/jama.288.3.321.

³² Wyeth Pharmaceuticals, "FDA Approves Prescribing Information for Postmenopausal Hormone Therapies," accessed March 31, 2017, <https://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM168819.pdf>.

higher for unapproved, compared with approved uses of prescription drugs. Additionally, the risk of adverse drug events was highest for off-label use without strong scientific evidence.³³

2. Early clinical trial results can be misleading

The role of large phase III confirmatory trials in the clinical research process is important. Even accurate representations of clinical trial data can be misleading if the study is not adequately powered to establish efficacy or detect potential harms.³⁴ There have been numerous instances when large late-stage clinical trials have failed to support the findings of smaller early studies.³⁵

For example, in 2006, Pfizer's promising drug to treat heart disease, torcetrapib, was tested in a phase II trial and shown to improve cholesterol levels in patients with a history of cardiovascular disease. Specifically, treatment raised HDL ("good") cholesterol levels and lowered LDL ("bad") cholesterol levels, compared to placebo.³⁶ However, when Pfizer tested torcetrapib in a phase III trial that randomized over 15,000 participants, not only did the drug not prove to be effective for treating heart disease, but it also proved to be unsafe. Patients who received torcetrapib were significantly more likely to suffer a major cardiac event or die from any cause than those taking placebo.³⁷ As a result of these safety concerns, the trial was stopped early.³⁸

More recently, Eli Lilly tested its drug, solanezumab in a series of phase III trials, after promising phase II trials results showed improvement in biomarkers associated with Alzheimer's disease. The results of two large phase III trials in 2012 failed to show effectiveness in treating patients with mild or moderate Alzheimer's disease, but suggested the drug might have an effect among a subgroup of patients with mild dementia caused by Alzheimer's.³⁹ In 2016, Eli Lilly halted a third large phase III trial, based on results

³³ Tewodros Eguale, et al., "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population," *Journal of the American Medical Association Internal Medicine* 176, no. 1 (2016): 55-63, doi:10.1001/jamainternmed.2015.6058.

³⁴ For this reasons, three phases of clinical trials are required. Phase I clinical trials test how well the drug is tolerated among a small group of individuals — often patients who have tried and failed to improve with standard therapies — and determine a safe dosage range. Phase II trials further evaluate the drug's safety and assess its effectiveness among a larger sample — typically a few hundred individuals. Because of their short duration, many Phase II trials measure biomarkers or surrogate endpoints, rather than clinical outcomes. Phase III trials, which test the drug in a larger group of individuals for a longer duration, typically measure clinical outcomes, and are therefore more representative of how the product might be used in clinical practice. Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, *Fundamentals of Clinical Trials*, 3rd Ed. (New York: Springer-Verlag, 1998), 3-5. See, e.g., 21 CFR 312.21.

³⁵ Thomas J. Hwang, et al., "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results," *Journal of the American Medical Association Internal Medicine* 176, no. 12 (2016): 1826-1833, doi:10.1001/jamainternmed.2016.6008.

³⁶ Michael H. Davidson, et al., "Efficacy and Safety of Torcetrapib, a Novel Cholesteryl Ester Transfer Protein Inhibitor, Individuals with Below-Average High-Density Lipoprotein Cholesterol Levels," *Journal of the American College of Cardiology* 48, no. 9 (2006): 1774-81, doi:10.1016/j.jacc.2006.06.067.

³⁷ Phillip J. Barter, et al., "Effects of Torcetrapib in Patients at High Risk for Coronary Events," *New England Journal of Medicine* 357, no. 21 (2007): 2109-22, doi:10.1056/NEJMoa0706628.

³⁸ Ibid.

³⁹ Rachelle S. Doody, et al., "Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease," *New England Journal of Medicine* 370 (2014): 311-21, doi:10.1056/NEJMoa1312889.

showing that patients treated with the drug experienced a slowing of cognitive decline that was not statistically different than the patients treated with placebo.⁴⁰

According to one review, 55 percent of drugs in clinical development between 2012 and 2015 failed phase III trials due to insufficient efficacy and 14 percent failed due to safety reasons.⁴¹ In an analysis, published by FDA in January 2017, of 22 case studies of medical products in which promising Phase II clinical trials results were not confirmed in Phase III clinical testing, there were 14 cases that failed on efficacy, one case that failed on safety, and 7 cases that failed on both safety and efficacy.⁴²

Because it would be impractical for firms to do phase III clinical trials to test every new indication of their product, health care providers are often left to extrapolate evidence from existing trials. While the above examples reference drugs that were never approved by FDA, they illustrate that even if early results are promising, the public may be at risk of receiving unsafe or ineffective treatments if firms are permitted to promote products for off-label uses with inadequate evidence.

3. Independent scientific review informs provider decisions

Physicians have access to a wealth of scientific information from a variety of sources, including clinical trials and reviews in the peer-review literature, information disseminated by academic organizations and professional societies, as well as unpublished research presented at scientific conferences.

However, the quality of this evidence varies. Even scientific information in peer-reviewed journal articles, considered to be a high standard for evaluation of work, has limitations, which have been extensively documented.⁴³ Therefore, FDA's independent pre-market review process is well suited to establish safety and efficacy of medical products for each of their intended uses.

Research shows that peer-reviewed journals have a tendency to publish positive results. For example, one review found that clinical trials with positive findings (defined as either those that were statistically significant, perceived to be important or striking, or indicating a positive effect) were nearly four times more likely to be published, compared to findings that were not positive.⁴⁴ A second study compared the results of pre-market reviews conducted by FDA for 12 antidepressant agents with matching publications in the literature. Among 74 FDA-registered studies, trials that FDA judged as positive for the purposes of approvals with respect to meeting the pre-specified primary endpoints were approximately 12 times more likely to be published as were non-positive results. Strikingly, even studies that were not judged as

⁴⁰ Ely Lilly, "Lilly Announces Detailed Results of Solanezumab Phase 3 EXPEDITION3 Study at the Clinical Trials on Alzheimer's Disease (CTAD) 2016 Meeting," accessed March 31, 2017, <https://investor.lilly.com/releasedetail.cfm?ReleaseID=1003490>.

⁴¹ Richard K. Harrison, "Phase II and Phase III Failures: 2013-2015," *Nature Reviews Drug Discovery* 15 (2016): 817-18, doi:10.1038/nrd.2016.184.

⁴² U.S. Food and Drug Administration, "22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results," accessed April 7, 2017, <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf>.

⁴³ John P.A. Ioannidis, "Why Most Published Research Findings Are False," *Public Library of Science Medicine* 2, no. 8 (2005): 0696-0701, doi:10.1371/journal.pmed.0020124 and Shaniel Ebrahim et al., "Reanalyses of Randomized Clinical Trial Data," *Journal of the American Medical Association* 213, no. 10 (2014): 1024-32, doi:10.1001/jama.2014.9646.

⁴⁴ Sally Hopewell et al., "Publication Bias in Clinical Trials Due to Statistical Significance or Direction of Trial Results," *Cochrane Database of Systematic Reviews* (2009):1, doi:10.1002/14651858.MR000006.pub3.

positive according to FDA's conclusion were published in a way that conveyed a positive outcome for 15 percent of the studies.⁴⁵

Industry-sponsored research, in particular, may result in selective promotion of results. Industry has a compelling financial incentive to promote their approved products for additional unapproved uses, and financial disclosures do not fully mitigate conflict of interest concerns. Studies show that industry sponsorship leads to publishing of more favorable results.⁴⁶ Even if negative results are published for a medical product, firms have no incentive to distribute that information to healthcare providers. Selective promotion could lead to an unbalanced and incomplete overview of the evidence describing the risks and benefits of a medical product.

FDA review protects against the risks of publication bias and not comparing results to the planned trial protocol, because FDA reviewers see the entire data package and can compare it with the study protocol. Peer review does not protect against these risks, and the quality of peer review is variable.⁴⁷ Specifically, studies have shown that peer reviewers were unable to detect errors in reporting findings (i.e., distorting non-significant results)⁴⁸ or improve the completeness of reporting.⁴⁹ There are no accepted standards for journal peer review, and reviewers almost never see the study protocol, so they cannot tell whether the reported findings and analysis methods reflect the investigators' intent. In contrast, when considering data for potential inclusion in a medical product's labeling, FDA independently reviews the study protocol. Similarly, while peer reviewers typically do not have access to the full dataset supporting a publication, FDA reviews all of the data and other appropriate scientific evidence.

Peer-reviewed publications are an essential support for clinical decision-making, but does not, and should not, mean that companies should be able to promote their products for uses supported only by this type of evidence. For the purposes of ensuring that patients are not treated with products for unsafe or ineffective uses, a more rigorous review process is required that involves access to complete data to evaluate off-label indications. When using medical products for an approved use, healthcare providers have assurance that their treatment decisions are based not only on robust evidence, but also on the quality, rigor, and independence of the evaluation of that evidence.

Conclusion

The lines between off-label and on-label communications are not always clear, and there are both potential benefits and concerning risks to communications that go beyond approved uses. As FDA considers updates to its regulations and policies governing firms' communications about unapproved uses of approved medical products, FDA should consider the following:

⁴⁵ Erick H. Turner, et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," *New England Journal of Medicine* 358 (2008): 252-60, doi:10.1056/NEJMsa065779.

⁴⁶ Andreas Lundh et al., "Industry Sponsorship and Research Outcome," *Cochrane Database Systematic Reviews* 12 (2012): 1-88, doi:10.1002/14651858.MR000033.pub2.

⁴⁷ Tom Jefferson, Elizabeth Wager, and Frank Davidoff, "Measuring the Quality of Editorial Peer Review," *Journal of the American Medical Association* 287, no. 21 (2002): 2786-90, doi:10.1001/jama.287.21.2786.

⁴⁸ Isabelle Boutron, et al., "Reporting and Interpretation of Randomized Controlled Trials with Statistically Nonsignificant Results for Primary Outcomes," *Journal of the American Medical Association* 303, no.20 (2010): 2058-64, doi:10.1001/jama.2010.651.

⁴⁹ Sally Hopewell, et al., "Impact of Peer Review on Reports of Randomized Trails Published in Open Peer Review Journals: Retrospective Before and After Study," *British Medical Journal* 349 (2014): g4145, doi:10.1136/bmj.g4145.

1. The quality and rigor of published literature, even peer-reviewed literature is variable. Selective publication of studies, or of outcomes within studies, can create misleading impressions of a product's safety and effectiveness.
2. FDA reviewers are unique in that they have access to the complete underlying data supporting firms' claims, the study protocol, and the scientific expertise to determine whether proposed claims are supported by the clinical evidence. Peer review alone does not fulfill this role.
3. FDA's authority to require substantiation for claims about a product will be considerably undermined if firms may offer products for sale (i.e., promote) for off-label uses without first providing that substantiation.
4. FDA plays a critical role in ensuring that providers and the public know whether products work and potential harms associated with each of the uses for which products are being promoted.

The Pew Charitable Trusts appreciates the opportunity to comment on FDA's efforts to engage in a comprehensive review of its regulations and policies governing firms' communications about unapproved uses of approved medical products. Given the importance of scientific integrity in the information used by healthcare providers in making treatment decisions, and the important role of the FDA in protecting patient safety, FDA review provides important safeguards in reducing harm from unproven uses of approved products. We thank the agency for its consideration of our comments.

Sincerely,



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