

FDA Hearing – Communications about Off-Label Uses
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My name is Amy Kapczynski, and I am a Professor of Law at the Yale Law School. I am also a faculty director of the Collaboration for Research Integrity and Transparency (CRIT). In my comments, I will address the developments in constitutional law that the FDA is likely grappling with, as it determines whether it ought to depart substantially from its historical approach to off-label promotion.

To begin, it is important to understand two basic things about First Amendment law. First, commercial speech is not entitled to the same degree of protection as political speech and thus, may be, and is, much more extensively regulated than is political speech. The Supreme Court's governing *Central Hudson* test permits government to regulate commercial speech in order to ensure that the public has access to not only information, but accurate information. This is why, for example, while the government cannot bar false political speech, it can bar false commercial speech.

Second, for decades, no court indicated that the FDA's core restrictions on off-label promotion were in any tension with the First Amendment. That changed in 2012, when by a vote of two to one, a panel of judges on the U.S. Court of Appeals for the Second Circuit, in a case called *U.S. v. Caronia*, invalidated the conviction of a drug company representative for promoting a drug off-label.¹ In that case, a pharmaceutical detailer had promoted a drug (sodium oxybate, or *Xyrem*), approved to treat narcolepsy, for off-label uses including chronic pain. The Second Circuit concluded that the government could not prosecute the detailer simply for making promotional statements about off-label uses. But

¹ *U.S. v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

it was also careful not to entirely strike down the FDA's authority to regulate off-label promotion. While the court decided that the government could not penalize speech itself, it suggested that the government might have prevailed if it argued that it was penalizing conduct – the conduct of selling a misbranded drug – and only using speech as evidence of that crime. This reflects a general rule in First Amendment law, that speech can be used as evidence of a crime. (Consider hate crimes: A racist statement can be penalized in this setting because it is evidence of forbidden intent.)

In 2015, however, a trial court in the Southern District of New York went further than this, in a case called *Amarin Pharma, Inc. v. FDA*, and concluded that the FDA did not have authority to prohibit off-label speech unless that speech is false or misleading, rejecting the “evidentiary” argument left open in *Caronia*.² The FDA settled that case, so the trial court's conclusion was not reviewed by an appellate court.

I want to make three simple points about these two cases.

First: these cases do not represent a definitive resolution of the issue. The *Caronia* decision was deliberately modest in its reach, and pointed to an alternative argument that could immunize the agency's historical approach. That “evidentiary” argument is a powerful one. It is one, in fact, that many courts of appeals have accepted as the very basis of the FDA's power to regulate unapproved medicines: A company that markets an entirely unapproved drug cannot argue that its treatment claims are constitutionally protected speech, making the agency disprove them.³ The court in *Amarin* disagreed with the argument, but it is only a trial court decision, and does not bind other courts, even in the same jurisdiction. There are other arguments that the FDA can press in future

² *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

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

prosecutions, and before an appeal to the Supreme Court. As I described, the government is allowed to regulate commercial speech to ensure that the public is adequately informed. Properly understood, the FDA's historical approach serves this end, because it is well-tailored to a substantial need: the production of high quality evidence, that can then be reviewed by expert regulators.

Second, these cases illustrate the very real dangers of a legal standard that permits any off-label speech as long as it is not "false and misleading." This standard, I fear, will not be interpreted by courts in a manner that requires rigorous evidence. Judges may, for example, see any evidence – including animal studies, or worse – to be the basis for statements such as "some evidence supports the use of this drug for X condition." The dietary supplements context, where these First Amendment arguments emerged many years ago, provides a warning. In a 2001 case about folic acid in the D.C. district court called *Pearson v. Shalala*, the judge concluded that the FDA could not prevent a health claim as misleading even though the agency had concluded there was a lack of evidence in support of the claim, because, and I quote, "The mere absence of significant affirmative evidence in support of a particular claim ... does not translate into negative evidence against it."⁴ That is not how the scientific method works, but of course judges are not trained in the scientific method. If the FDA revises its approach to medicines in the way that some have urged it to do, we may very well end up with a drug industry that looks more like the supplements industry.

Third, and finally, in its hearing announcement the FDA signaled that it may be considering changing its approach not merely to marketing to doctors, but also to

⁴ *Pearson v. Shalala*, 130 F. Supp. 2d 105 (D.D.C. 2001).

marketing direct to consumers. I want to stress that both of these two cases considered marketing only to doctors, and in both cases, the court's constitutional analysis turned on the purported sophistication of this audience. I do not believe that either court would have come to the same conclusion had the communications at issue been direct to consumers. Commercial speech standards, precisely because they are meant to protect informational quality, give the agency ample room to restrict statements to consumers that might be permitted to doctors, given the heightened potential that lay audiences will misunderstand marketing statements.

I hope that these brief remarks will help to reassure the agency that its long-standing approach may well still be upheld in the courts. Given the stakes, I also urge the agency to continue enforcing its authority over off-label promotion, and in an appropriate case to defend it fully, including at the Supreme Court.

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Jeanie Kim, Research Fellow
Collaboration for Research Integrity and Transparency
Yale Law School

My name is Jeanie Kim, and I am a research fellow at the Collaboration for Research Integrity and Transparency (CRIT). I will be making three points today: First, permitting the promotion of off-label uses reduces incentives for drug firms to invest in clinical research and produce strong evidence for new indications. Second, expanding the “safe harbor” in the agency’s current guidance for off-label communications will give firms greater freedom to market off-label uses under the guise of “disseminating scientific findings.” Finally, the agency should strengthen, not weaken, its standards by requiring greater research transparency when drug firms disseminate information about off-label uses.

There has been increasing pressure on the agency to relax its stance on drug firms’ communications about unapproved uses. However, the FDA’s authority to prohibit pharmaceutical promotion of unapproved uses is a critical component of its regulatory system – a system established in 1962 when Congress granted the FDA the authority to require drug firms to demonstrate a drug’s safety and efficacy with respect to each indication. It was this grant of authority that set forth the framework for drug firms to design rigorous clinical studies, test the validity of specific drug claims, and generate the evidence base for medical products. By restricting drug firms from making claims about off-label uses and by requiring regulatory review and approval for each intended use, the FDA encourages firms to invest in clinical studies and produce strong scientific evidence that supports new uses of medicines. Off-label promotion undermines this system – it undermines the production of evidence and the regulatory review of evidence.

While the prescription of drugs for off-label uses is permitted and prevalent in clinical practice, off-label uses are often not supported by adequate evidence.¹ This gap in evidence has clinical and economic consequences for patients and the healthcare system.² If an off-label use is promising, then it should be rigorously tested and validated with controlled clinical studies and subject to independent scrutiny by the FDA and its outside advisors. Strong clinical evidence is necessary to separate truly promising off-label uses from those that do not live up to their promises.

However, the gap in evidence for off-label uses is less likely to be filled if companies are permitted to make promotional statements about off-label uses. If drug firms can increase sales and expand the market for an approved medicine by promoting unapproved uses, there is less incentive to invest the time and resources to conduct the trials necessary for new use approval. In fact, drug firms may have the incentive not to conduct rigorous trials for off-label uses as there is a risk that the evidence will not work in their favor. Permitting off-label promotion encourages drug firms to obtain approval for one narrow indication and then widen the market for the drug without producing strong evidence to justify the additional benefit claims, or without demonstrating that the benefits outweigh the risks or that there are even benefits at all.

In addition to undermining firms' incentives to test and validate off-label uses, off-label promotion might reduce patients' willingness to participate in clinical trials. When off-label uses are widely promoted, thereby increasing prescriptions and demand, those off-label uses then become the standard of care, discouraging patients from joining trials that do not guarantee access as comparisons with placebos or alternatives are critical in clinical studies.

¹ Radley DC, Finkstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006;166(9):1021-1026. doi:10.1001/archinte.166.9.1021.

² Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med.* 2016;176(1):55-63. doi:10.1001/jamainternmed.2015.6058.

The FDA already allows drug companies to engage in limited communications about unapproved uses by drawing a distinction between “promotion” and “scientific exchange.”³ Drug firms are permitted to respond to unsolicited requests for off-label information as long as the responses are scientific in nature, not promotional, and generated by medical or scientific personnel independent from sales or marketing departments.⁴ They are also permitted to distribute scientific or medical journal articles on unapproved uses as long as such articles are peer-reviewed and based on adequate and well-controlled clinical investigations.⁵ Over the years, the agency has shifted the line between “promotional statements” and “dissemination of scientific findings.” For example, in 2014, the FDA revised its guidance to allow drug firms to disseminate non-peer-reviewed clinical practice guidelines containing information about off-label uses. Here, with the request for comments on off-label communications, the agency seems to again contemplate where and how to draw that line, potentially opening more modes of communication to fall under the safe harbor of scientific exchange

Drug firms should not be permitted more ways to communicate about off-label uses under the guise of “disseminating scientific findings.” And they should not be permitted to circulate off-label information on the basis of less or weaker evidence. Already, the distinction between promotion and scientific exchange is blurred by widespread pharmaceutical practices, such as the practice of reprints and seeding trials, trials designed solely for marketing purposes rather than for rigorous inquiry into risks and benefits. There has been a push by the industry and some members of Congress to allow more communications about off-label uses under the safe

³ 21 C.F.R. § 312.7.

⁴ US Food and Drug Administration. Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices. Draft Guidance (2011).

⁵ US Food and Drug Administration. Distributing Scientific and Medical Publications on Unapproved New Uses. Draft Guidance (2014).

harbor of “scientific exchange.” But, broadening the categories of what constitutes “scientific exchange” or weakening its standards will give firms more freedom to disseminate information that distorts medical evidence.

We urge the agency to add more safeguards to ensure that information that drug companies are currently permitted to disseminate can be rigorously scrutinized. Even current safeguards, such as mandating disseminated articles to be peer-reviewed and published in medical journals, do not always ensure that the underlying studies were well designed and rigorously conducted or that the results are sound. Nor are they sufficient when taking into account publication biases or reprints. Drug firms can selectively communicate information to physicians, and the lack of transparency makes it difficult to assess the validity of the evidence in published literature. While these problems exist regardless of whether the studied use is approved or unapproved, it is all the more problematic for the dissemination of information about off-label uses as the uses have not been independently scrutinized and determined by the agency to be supported by aggregate evidence.

The agency should require greater research transparency by ensuring registration and reporting on ClinicalTrials.gov (and even data sharing) for the studies underlying drug firms’ communications about off-label uses as well as any studies involving that drug. Drug firms seeking to distribute articles about off-label uses should certify compliance with registration and reporting requirements for all clinical studies for that product, particularly studies implicating off-label uses, so that investigators and clinicians have access to results for a range of trials, and not just those selectively published and distributed by the drug firm.

We emphasize the need for greater transparency given the FDA’s current guidance on off-label communications, but transparency cannot be a substitute for evidence production –

transparency does little to improve the evidence base for new uses of medicines if clinical studies for new uses are not conducted in the first place. Nor should transparency be a replacement for strong regulatory standards. Only regulators have full access to underlying clinical data; registering and reporting on ClinicalTrials.gov and publishing studies cannot substitute for rigorous regulatory scrutiny. The agency should maintain its restrictions on off-label promotion, including the dissemination of information about off-label uses that are unsubstantiated or based on weak or incomplete evidence, to ensure that each use that is promoted by a drug firm has been demonstrated to be safe and effective based on strong clinical evidence.

The FDA has an obligation to ensure the safety and efficacy of medical products, a determination that can only be made on the basis of strong scientific evidence. The agency would be failing its statutory duties to protect patients and the public if it voluntarily relinquished its authority over off-label communications, knowing that it would compromise the evidence base for medicines.

**FDA Hearing – Communications about Off-Label Uses
Margaret McCarthy, Executive Director
Collaboration for Research Integrity and Transparency
Yale Law School**

I am Margaret McCarthy, the executive director of the Collaboration for Research Integrity and Transparency, a joint initiative of Yale Law School, Yale School of Medicine, and Yale School of Public Health. Our mission is to promote health by improving the integrity and transparency of biomedical and clinical research, and we are dedicated to ensuring that the evidence base for medical products is complete, accurate, and available for scientific and public health inquiry. I'm here with Jeanie Kim, research fellow at CRIT, who will address the impact of off-label promotion on the evidence base for medicines, and Amy Kapczynski, law professor and faculty co-director of CRIT, who will address the First Amendment challenges raised by the pharmaceutical industry. As for disclosures, CRIT is funded by a research grant to Yale University from the Laura and John Arnold Foundation. The sponsor had no role in the content of our testimonies or in our decision to testify. Our testimony also does not purport to present Yale's institutional views.

My comments will address the risk that off-label marketing by medical product companies has for the patient-medical provider relationship. This risk applies to both off-label communications to members of the public, and to health care providers.

CRIT encourages the availability of high quality, accurate scientific information regarding medical products. Consumers need access to accurate, evidence-based information regarding medical products so that they can make the best possible medical decisions for themselves, in partnership with health care providers. Any marketing directly to consumers by

medical product manufacturers regarding off-label use should be prohibited as contrary to this principle.

The FDA's role in protecting the public by ensuring that drugs, biologics and high risk medical devices are safe and effective for approved uses, before they reach the market, is key to the ability of consumers to trust the medical products on the market, and to trust that the benefits of taking a drug or biologic for an approved purpose outweigh the risks. Health care providers similarly rely on the FDA to ensure that the medical products that they may prescribe are safe and effective.

It is important to point out that medical providers in the U.S. have always been free to prescribe medical products for off-label use when they deem it appropriate. Indeed, in some limited circumstances, evidence-based guidelines and practice parameters have included recommendations for off-label medical product prescribing. Off-label prescribing is appropriate where there is informed consent, where the prescriber is well-versed in the condition for which the medication is prescribed, where there is a robust literature on safety and risk-benefit analysis in the population affected, and an adequate literature regarding efficacy for the condition treated.¹

Where this evidence base is lacking, patients run the risk of being exposed to unsafe and/or ineffective medical products. This is especially true for special populations, such as children and the elderly.² Concerns regarding the lack of evidence for use of adult medical

¹ Vox, F., Capron, A. M., Kraus, M. F., Alexander, G. C., & Kirschner, K. L. Balancing Burdens and Benefits: Ethical Issues of Off-Label Prescription. *PM&R*. 2013;5(10):882-889. doi: <http://dx.doi.org/10.1016/j.pmrj.2013.08.601>.

² Zito, J. M., Derivan, A. T., Kratochvil, C. J., Safer, D. J., Fegert, J. M., & Greenhill, L. L. (2008). Off-label psychopharmacologic prescribing for children: History supports close clinical monitoring. *Child and Adolesc Psychiatry and Mental Health*. 2008;2(1):24. doi:10.1186/1753-2000-2-24; Czaja, A. S., & Valuck, R. Off-label antidepressant use in children and adolescents compared with young adults: extent

products in children, despite extensive off-label prescribing, led to the passage of the Pediatric Research and Equity Act and the Best Pharmaceuticals for Children Act, so that medical products approved for adults would also be evaluated for safety and efficacy in pediatric populations.

Promotion by manufacturers of off-label uses to medical professionals upsets the balance of informed medical decision-making. The majority of prescriptions in the U.S. are written in primary care settings. It has been estimated that it would take more than 600 hours per month for a primary care provider to review all of the relevant new literature.³ Additionally, a national random survey of physicians revealed that they had difficulty distinguishing between off-label use supported by evidence and approved uses for medication, and that 41% of those surveyed believed that an off-label use with little or no evidence to support it was actually an approved use.⁴

Prescribing patterns are clearly influenced by off-label promotion. In the past two decades, we have seen large classes of medication improperly promoted for off-label use, often with devastating results. The off-label marketing of anti-depressants for children and adolescents that had only been approved for adults, and of atypical antipsychotics for elderly patients with dementia, are only two examples of many that were associated with an increase in

and level of evidence. *Pharmacoepidemiology and Drug Safety*. 2012;21(9):997–1004. doi:10.1002/pds.3312.

³ Alper, B. S., Hand, J. A., Elliott, S. G., Kinkade, S., Huan, M. J., Onion, D. K., & Sklar, B. M. How much effort is needed to keep up with the literature relevant for primary care? *J Med Library Association*. 2004;92(4):429-437.

⁴ Chen, D. T., Wynia, M. K., Moloney, R. M., & Alexander, G. C. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidemiology and Drug Safety*. 2009;18(11): 1094-1100. doi: <http://dx.doi.org/10.1002/pds.1825>.

off-label prescribing and well-documented increased morbidity and mortality.⁵ Clearly, in these examples, the risks of off-label use outweighed the benefits.

Allowing manufacturers to promote off-label uses to consumers, whether on the Internet or by other means, will not provide consumers with high quality, science-based information to make truly informed medical decisions. Only the U.S. and New Zealand allow any direct advertising of medical products to consumers. Under current law and policy, such direct to consumer marketing in the U.S. is limited to approved uses. CRIT urges the FDA to reject any modification of current policy that would allow direct communication to consumers and expand communication to medical providers regarding unapproved uses. Indeed, the leading pharmaceutical industry trade group, PhRMA in the U.S., has adopted guiding principles that exclude off-label direct to consumer marketing. In Europe, the pharmaceutical industry trade group EFPIA, opposes all promotion of off-label use, regardless of audience.

We oppose any changes that would permit more freedom for the pharmaceutical industry to engage in communications about off-label uses. We support the agency's longstanding authority to regulate such communications and recommend that any changes that the agency implements will strengthen, and not weaken, its regulations and policies.

⁵ Food and Drug Administration. FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medications. May 2, 2007. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108905.htm>; Government Accountability Office. Antipsychotic Drug Use: HHS Has Initiatives to Reduce Use among Older Adults in Nursing Homes, but Should Expand Efforts to Other Settings (GAO Publication No. GAO-15-211). Washington, D.C.: U.S. Government Printing Office. 2015. Available at: <http://www.gao.gov/products/GAO-15-211>.