UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., *et al.*,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	No. 1:15-cv-03588-PAE
	)	
UNITED STATES FOOD & DRUG ADMINISTRATION, *et al.*,	)	ECF Case
	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OF AMICUS CURIAE PUBLIC CITIZEN, INC., IN SUPPORT OF THE FDA AND IN OPPOSITION TO THE MOTION FOR PRELIMINARY INJUNCTION

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INTEREST OF AMICUS CURIAE[1]

Amicus curiae Public Citizen, Inc., is a non-profit organization with more than 300,000 members and supporters nationwide. Public Citizen has a longstanding interest in public health, including drug safety and FDA regulation. Public Citizen's Health Research Group (HRG) promotes research-based, system-wide changes in health care policy and provides oversight concerning drugs and medical devices, among other things. Public Citizen's Litigation Group has frequently participated in cases arising from the pharmaceutical and medical device industries' marketing of unsafe drugs and medical devices. *See*, *e.g.*, *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996). Public Citizen therefore has substantial experience with the regulatory background of this case.

In addition to its interest in drug regulation and health issues, Public Citizen has significant interest and expertise in commercial-speech doctrine. Public Citizen has represented parties seeking to invalidate overbroad restraints on commercial speech when those restraints harmed competition and injured consumers, including in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976), and *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626 (1985). It has also defended commercial-speech regulations in cases where they were important to protecting the public health or served other important state interests,

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[1] No counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. No one other than amicus curiae made a monetary contribution to the preparation or submission of this brief.

for example in *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 561 (2001), and *National Ass'n of Manufacturers v. SEC*, 748 F.3d 359 (D.C. Cir. 2014) (rehearing pending following overruling in part by *Am. Meat Inst. v. Dept. of Agric.*, 760 F.3d 18 (D.C. Cir. 2014)). Public Citizen offers a consumer perspective on both the regulatory and speech issues presented here, different from that of either of the parties.

ARGUMENT

I. The arguments of Amarin and its amici are inimical to a regulatory scheme premised on the requirement that manufacturers obtain FDA approval to market new drugs.

Amarin and its amici in this case advance a proposition that is stunning in its implications: that federal laws and regulations providing that prescription drugs can be introduced in commerce only if intended for uses approved by the FDA are a form of content- and speaker-based regulation of speech subject (in the view of some of the amici) to strict scrutiny. As the FDA explains, that proposition, if accepted, would grant a drug manufacturer the presumptive ability to market a drug for any use once it has received FDA approval for a single use, with the burden on the FDA to prove that the manufacturer's marketing was deceptive or that the drug was unsafe for that use. But the implications do not stop there. Taken seriously, the proposition that introducing a substance into commerce for a particular purpose is speech fully protected by the First Amendment would imply that, unless it were otherwise unlawful to manufacture or sell a substance, a manufacturer could market it as a drug, with no approval at all, and its conduct in so doing would receive First Amendment protection unless the government bore the burden of showing that prohibiting the marketing of the drug satisfied strict scrutiny. Such a result would

overturn the carefully constructed, decades-old regulatory structure governing pharmaceuticals, which is premised on the FDA's expertise in determining whether to permit marketing only of drugs that manufacturers have proven to be safe and effective for their intended use.

The heart of the federal regulatory regime governing prescription drugs since the 1962 amendments to the Food, Drug, and Cosmetic Act (FDCA) has been the requirement that manufacturers bear the burden of proving both safety and efficacy of their drugs to obtain FDA premarket approval to sell them:

> In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer. Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" before it could distribute the drug. … In addition, the amendments required the manufacturer to prove the drug's effectiveness by introducing "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Wyeth v. Levine, 555 U.S. 555, 567 (2009) (quoting provisions now codified at 21 U.S.C. § 355(d)). As the FDA's memorandum opposing the motion for preliminary injunction explains at greater length (at pp. 12–13), the interlocking provisions of the FDCA and its implementing regulations establish that if a manufacturer places a drug into commerce with the intent that it be given an unapproved use, the manufacturer violates the FDCA's prohibition on introduction of an unapproved new drug. 21 U.S.C. §§ 331(d), 355(a). Marketing a drug with such intent will also violate

the prohibition on misbranding a drug, *id*. § 331(a) & (b), as the drug's approved labeling will lack adequate directions for the unapproved use. *See id.* § 352(f)(1).

As is generally true of a person's or company's intent, the intent with which a drug manufacturer introduces its products into commerce must be inferred, and a pharmaceutical company's statements in promoting its drugs are a primary source of evidence about its intent. *See United States v. An Article Consisting of 216 Cartoned Bottles, More or Less*, 409 F.2d 734, 739 (2d Cir. 1969) ("It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source."). Here, Amarin makes no bones about the fact that it intends to market Vascepa to doctors for the unapproved—indeed, affirmatively rejected—use of lowering persistently high triglyceride levels in patients who use statins to reduce low-density lipoproteins ("bad cholesterol"). Amarin contends, however, that because it will manifest that intent through commercial speech aimed at encouraging doctors to prescribe Vascepa for an unapproved use, its marketing is entitled to First Amendment protection. Indeed, Amarin's amici contend that Amarin is entitled to the highest level of First Amendment protection and that restrictions on its efforts to market Vascepa for an unapproved use are subject to strict scrutiny under the Supreme Court's ruling in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), because they are supposedly speaker- and content-based restrictions on speech.

Amarin relies principally on the Second Circuit's decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), but the holding of *Caronia* was only that the

FDCA does not outlaw promotional speech in and of itself. If it did, the court held, its application to the facts of that case would not have comported with the First Amendment. *See id*. at 161–62. The court carefully did not hold that using speech to establish a pharmaceutical company's intent to introduce a drug into commerce for an unapproved use would violate the First Amendment—indeed, it explicitly stated its assumption that "such use of evidence of speech is permissible." *Id*. at 162 n.9.[2] *Caronia*'s assumption was firmly grounded in the Supreme Court's holding in *Wisconsin v. Mitchell*, 508 U.S. 476 (1993), that "[t]he First Amendment … does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." *Id*. at 489; *see also United States v. Pierce*, 785 F.3d 832, 841 (2d Cir. 2015); *United States v. Salameh*, 152 F.3d 88, 112 (2d Cir. 1998); *United States v. Kaziu*, 559 F. App'x. 32, 35 (2d Cir. 2014).

Sorrell likewise lends no force to Amarin's claim of First Amendment protection. First, the state law at issue in *Sorrell*, unlike the FDCA, did not restrict the marketing of a non-speech product based on the marketer's intent; it *directly* restrained speech—the dissemination of information. 131 S. Ct. at 2667. Moreover, even if the marketing of a drug with the intent that it be put to an unapproved use were subject to First Amendment protection, it would not follow that *Sorrell* would

[2] The court further stated that it would be "unclear" whether a manufacturer's mere knowledge that a doctor intended to put a drug to an unapproved use would establish an illicit intent by the manufacturer in distributing the drug. 703 F.3d at 162 n.9. This case presents no such unclarity, for Amarin has made clear its intention to market the drug for an unapproved use.

command the application of strict scrutiny. *Sorrell* held that a law that placed content- and speaker-based burdens on pharmaceutical manufacturers' commercial speech was subject to what it called "heightened scrutiny," *id*. at 2659, but the Supreme Court used that term to differentiate the scrutiny applicable in general to "expression protected by the Free Speech Clause of the First Amendment," *id*., from the rational-basis scrutiny applicable to non-speech economic regulation, which the state in *Sorrell* advocated. The Court did not use the term "heightened scrutiny" to specify a particular level of First Amendment scrutiny. To the contrary, it declined to determine whether strict scrutiny or the intermediate scrutiny applicable to commercial speech applied to the law at issue, as it held that the law could not be upheld under either standard. *See id*. at 2667; *see also Caronia*, 703 F.3d at 164 (stating that *Sorrell* "did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny"). Other courts have likewise concluded that *Sorrell* does not overturn established law that regulations of commercial speech are subject to a lesser standard of justification under the First Amendment than restrictions of non-commercial speech. *See*, *e.g.*, *Retail Digital Network, LLC v. Appelsmith*, 945 F. Supp. 2d 1119, 1124–25 (C.D. Cal. 2013); *King v. Gen. Info. Servs.*, 903 F. Supp. 2d 303, 307–09 (E.D. Pa. 2012).

The notion that the use of speech as evidence of someone's intent in distributing a product is not only subject to First Amendment scrutiny, but to strict scrutiny at that, would have broad consequences. Speech is used to discern intent, without First Amendment scrutiny, in a broad range of cases, including among others

criminal conspiracy, antitrust, and employment discrimination cases. In particular, it is not unusual for a person's intent concerning the commercial use of an item to have consequences with respect to whether his conduct is lawful or unlawful. The Supreme Court, for example, recently considered the federal Controlled Substance Analogue Enforcement Act, which makes unlawful the knowing manufacture or distribution (or possession with intent to distribute) of a substance that is similar in chemical structure and physiological effect to a federally listed controlled substance, if the substance is "intended for human consumption." *McFadden v. United States*, __ U.S. __, 2015 WL 2473377, at *4 (2015) (discussing 21 U.S.C. § 813). The Court in *McFadden* held that a conviction under the Act requires that the jury find the defendant possessed knowledge that the substance was an analogue of a controlled substance as well as intent that it be used for human consumption. *See id*. at *5. Unsurprisingly, the Court's opinion suggests no discomfort with the First Amendment implications of making the defendant's guilt depend on his intent with respect to the purchaser's use of the substance.

Under the view of the First Amendment taken by Amarin and its amici, however, the law would require First Amendment scrutiny if the government sought to prove a defendant's intent based on his statements that a buyer could get high if he used the analogue. Imposing liability where the defendant had promoted an analogue for such use but not where he had sold the substance for use as, say, an engine lubricant would, under the theory of Amarin and its amici, be a "content-based" restriction on speech. And punishing a manufacturer or distributor who had

advocated human consumption of a controlled substance analogue, but not a blogger who supported the use of the substance by humans, would in their view be a "speaker-based" speech regulation. A theory under which the use of speech to prove intent concerning the distribution of controlled substances would be subject to First Amendment scrutiny, let alone strict scrutiny, is dubious, to say the least.

More to the point here, Amarin's view of the First Amendment's scope would also have extremely broad implications for prescription drug regulation, as it would call into question the entire edifice of that regulatory regime. The regulatory regime is, at its most basic level, triggered by the introduction of a substance into commerce with the intent that it be used to diagnose, cure, mitigate, treat, or prevent disease or to affect the structure or function of the body. *See 216 Cartoned Bottles*, 409 F.2d at 739 ("Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims show intended uses that bring it within the drug definition."); *see also*, *e.g.*, *Whitaker v. Thompson*, 353 F.3d 947, 949–52 (D.C. Cir. 2004); *United States v. Cole*, __ F.3d __, 2015 WL 471594, at *3 (D. Or. Feb. 5, 2015); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1259–60 (S.D. Fla. 2005). It would, for example, be perfectly legal from the standpoint of the FDCA to introduce Vascepa into commerce as an indoor plant food: The FDCA would not classify the substance as a drug if sold with the intent that it be used in that manner, and hence it would not require FDA approval.

Amarin's First Amendment theory, however, suggests that if a manufacturer could lawfully market the substance for that non-drug use but, without approval,

could not lawfully market it for use to prevent disease, the imposition of criminal or civil liability on the manufacturer for selling the product as a drug without approval would require First Amendment scrutiny because liability would be based on the manufacturer's speech in promoting the product as a drug. *Cf. Caronia*, 703 F.3d at 180 (Livingston, J., dissenting). Moreover, according to Amarin, the restriction would be content-based because it was triggered by the substance of the manufacturer's speech (that is, that the speech encouraged use of the product as a drug rather than as fertilizer) and would also be speaker-based because someone who was not distributing the substance in commerce would be free to write articles or make speeches advocating that it be used as a drug. And according to Amarin's amici, the prohibition on selling an unapproved drug as a drug rather than as fertilizer would thus be subject to strict scrutiny, under which, they argue, the FDA would be required to prove either that the speech used to promote the drug was misleading or that the drug posed dangers that were sufficient to create a compelling interest in stopping the manufacturer from marketing it as a drug.

Assertions that the FDCA's fundamental requirement of premarket approval violates the First Amendment because it is based on an inference of intent from the manner in which a manufacturer markets a product have, where made directly, been rejected by the courts. *See Whitaker*, 353 F.3d at 953; *United States v. Cole*, 2015 WL 471594, at *4–5; *see also Holistic Candlers & Consumer Ass'n v. FDA*, 770 F. Supp. 2d 156, 164 & n.15 (D.D.C. 2011) (characterizing First Amendment challenge to requirement of premarket approval for medical device as "foreclosed by settled law

holding that use of speech to establish an element of a violation does not violate the First Amendment"), *aff'd on other grounds*, 664 F.3d 940 (D.C. Cir. 2012).

Amarin and its amici will undoubtedly disclaim any intention to make such a broad argument. But it is only a short step from the argument they make—that the First Amendment forbids the use of marketing statements to infer an intent to distribute a drug for an unapproved use—to the argument that it is unconstitutional to use such statements to infer intent to distribute a wholly unapproved drug. And the answer to both arguments is the same. "Assuming that the government may condition the sale of drugs on passage through the elaborate testing that the statute requires," *Whitaker*, 353 F.3d at 953, and given that whether a substance is a drug under the FDCA depends on its intended use, application of the *Mitchell* principle that intent may properly be inferred from speech leads to the conclusion that "it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining that … [the] proposed sale of [a particular substance] would constitute the forbidden sale of an unapproved drug." *Id*. Likewise, here, assuming the FDA may limit approval to particular uses for which a drug has been shown safe and effective, it is constitutionally permissible to use the manufacturer's speech to infer intent for purposes of determining whether its marketing would constitute the forbidden introduction of a drug for an unapproved use (or, what amounts to the same thing, a misbranded drug).

Acceptance of Amarin's arguments would thus contradict *Whitaker* and other decisions upholding the FDCA's prohibition on introduction into commerce of

unapproved drugs, and call into question the entire edifice of FDA regulation of drugs. Such a decision would be not only constitutionally unsound, but detrimental to important protections for public health and safety. The FDCA's requirement that manufacturers bear the burden of proving both the safety and efficacy of new drugs for their intended uses is critical to achievement of Congress's objectives of protecting the public against unsafe or worthless pharmaceutical products.

II. The requirement that manufacturers demonstrate both safety and efficacy serves vital public interests that are disserved by marketing of drugs with the intent that they be put to unapproved uses.

Congress established the first meaningful federal drug regulation in the Food and Drugs Act of 1906. The 1906 Act was a response to widespread fraudulent "patent medicine" schemes that promised cures for nearly any illness. Wallace F. Janssen, *Outline of the History of U.S. Drug Regulation & Labeling*, 36 Food Drug Cosm. L.J. 420, 422 (1981). The law gave the federal government authority to protect consumers by seizing adulterated or misbranded drugs, including drugs with labeling that is "false or misleading in any particular." 21 U.S.C. § 352(a). The 1906 law, however, did not require drug companies to perform any tests or submit any evidence to the FDA before promoting their drugs to the public, Richard A. Merrill, *The Architecture of Gov't Regulation of Med. Prods.*, 82 Va. L. Rev. 1753, 1761 (1996). Rather, it limited the FDA's enforcement authority to drugs that were already on the market. *Id*.

The lack of a pre-market approval process led to a public outcry in 1937, when a tainted antibiotic that the drug's manufacturer had never tested for safety killed

more than 100 people. *Id*. In response to the disaster, Congress passed the FDCA in 1938. *Id.* at 1761–62. The law required the manufacturer of a "new drug"—that is, a drug "not generally recognized among experts … as safe and effective for use"—to submit to the FDA, in advance of marketing a new product, a "new drug application" (NDA) demonstrating "substantial evidence" that the drug is safe for "use under the conditions prescribed" in its labeling. 21 U.S.C. §§ 321(p), 355(a), (b), (d). The law thus prohibited, for the first time, marketing a drug for any use not approved by the FDA.

In 1962, Congress enacted the next major amendment to the FDCA, this time inspired by the Thalidomide tragedy. Thalidomide, prescribed to pregnant women in Europe as a treatment for morning sickness, caused birth defects in hundreds of babies. The drug had been kept off the U.S. market by the vigilance of an FDA medical officer, but the tragedy sparked congressional hearings, which revealed that drug companies were making effectiveness claims that were unsupported or based on shoddy scientific evidence. FDA, *Promoting Safe and Effective Drugs for 100 Years*, http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm. The 1962 amendments require an NDA to include substantial evidence not only of a drug's safety, but also of its effectiveness for each intended use. 21 U.S.C. §§ 321(p), 355(a), (b), (d). This evidence must be supported by "adequate and well-controlled investigations." *Id.* § 355(d). Moreover, because a drug may be safe and effective for one use but unsafe or ineffective for another, the law requires a manufacturer of a drug that has already been approved

through an NDA to submit a supplemental NDA demonstrating the drug's safety and effectiveness for any additional use before labeling or promoting the drug for that new use. *See* 21 C.F.R. § 314.70. In this way, the regulatory scheme is crafted to provide an objective assessment of safety and effectiveness for *each* use for which the manufacturer intends to promote its product, *before* the manufacturer promotes the drug for patients' use.

The pre-market approval process is a cornerstone of modern health and safety regulation, serving the separate but complementary goals of protecting the public from dangerous drugs and preventing false and misleading claims. *See Abigail Alliance for Better Access to Dev'l Drugs v. von Eschenbach*, 495 F.3d 695, 703 (D.C. Cir. 2007) (en banc). Indeed, "[t]here are few, if any, more important functions performed by any regulatory agency than the function this case concerns—ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it." *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

The preeminent purpose of the NDA approval process is to protect the public from unsafe or ineffective drugs. *See* 21 U.S.C. § 393(b) (defining FDA mission as to "protect the public health"); *United States v. Lane Labs-USA Inc.*, 427 F.3d 219, 227 (3d Cir. 2005) ("[P]rotecting consumer health and safety is a primary purpose of the FDCA."). And the driving force behind both the 1938 and 1962 laws, which together

established the system of FDA pre-market review of drug safety and effectiveness, was significant injuries and deaths caused by dangerous drugs. *See* Merrill, 82 Va. L. Rev. at 1761–62. Through the NDA and supplemental NDA process, Congress sought to protect patients by detecting unsafe or ineffective medicines *before* they could be distributed to the public. *See* 21 U.S.C. § 321(p) (defining a "new drug" as a drug "not generally recognized among experts … as safe and effective for use"). The government's interest is at its maximum when protecting the health and safety of the public from products, such as drugs, that can injure or kill. *See Abigail Alliance*, 495 F.3d at 713 (recognizing the government interest in "protecting patients … from potentially unsafe drugs with unknown therapeutic effects").

The FDCA directly advances the interest in protecting the public by requiring a drug manufacturer, as a condition for sale in interstate commerce, to provide "substantial evidence" that its drug is both safe and effective for *each* intended use *before* promoting the drug for that use. 21 U.S.C. §§ 321(p), 355(a), (b), (d), (j). To meet the "substantial evidence" standard, a drug company must provide "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." *Id.* § 355(d). These standards "express well-established principles of scientific investigation," and the Supreme Court has held them "amply justified by the legislative history." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619 (1973). The statutory standard is further fleshed out by FDA regulations setting forth principles "recognized by the scientific

community as the essentials of an adequate and well-controlled clinical investigation." 21 C.F.R. § 314.126(a). These include steps to minimize bias, ensure selection of appropriate subjects and adequate controls, and exclude "[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation." *Id.* § 314.126(a), (b), (d), (e).

To the extent a manufacturer has evidence that a drug approved for one use is safe and effective for another, the statute and regulations provide a frequently used route to marketing the drug for that purpose: submission of a supplemental NDA for FDA review. *See* 21 C.F.R. § 314.70. Rather than relying on drug companies' unsubstantiated assertions, Congress and the FDA require drug companies to *prove* to an objective decisionmaker—the FDA—that their drugs are safe and effective for particular uses. The pre-market review process is a crucial bulwark against the sorts of pseudo-scientific evidence that were a hallmark of fraudulent medicine before the era of federal drug regulation. *See* Janssen, 36 Food Drug Cosm. L.J. at 422. The challenged regulatory scheme thus reflects Congress's and the FDA's reasonable conclusion that selling drugs for uses not validated by science is false or misleading and that, in light of the history of snake-oil salesmen touting products based on fraudulent or unproved claims, a system of objective scientific evaluation is needed to protect consumers. *See Bates v. State Bar of Ariz.*, 433 U.S. 350, 366 (1976) (noting that claims that are "not susceptible of precise measurement or verification … might well be deceptive or misleading to the public, or even false").

The regulatory scheme also reflects Congress's judgment that FDA review is needed before, rather than after, drug companies begin marketing drugs for new uses. That judgment is based on the experience that, in the absence of prior review, consumers could be injured or killed before the FDA has had a chance to discover that a drug is dangerous. The need for preapproval is especially compelling here because drug regulations "touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection." *United States v. Dotterweich*, 320 U.S. 277, 280 (1943). Patients lack both the expertise and the means to engage in the expensive and time-consuming process of evaluating drugs for safety and effectiveness, and physicians have neither time nor adequate data to make such an evaluation in the first instance. It therefore falls to the government to do so.

Moreover, the suggestion that, once the FDA has approved a drug for one particular use, the government lacks an interest in evaluating the drug's safety and efficacy for additional uses is fundamentally wrong. The FDA does not evaluate safety in a vacuum—as to each proposed use, the agency balances the drug's risks against its benefits for that use. *See* Richard A. Merrill, *Risk-Benefit Decisionmaking by the FDA*, 45 Geo. Wash. L. Rev. 994 (1977). For example, a drug that poses a serious risk to the patient's immune system may warrant approval to treat cancer if the risk is offset by the benefits of its effect on cancer, but not warrant approval to treat a headache. Moreover, the government has a powerful interest in ensuring that a drug is not only safe, but effective for every intended use. Even if a drug is

relatively safe for a particular unapproved use, a drug company's promotion of the product for that use can have serious health effects if it diverts a patient from a more effective treatment. *See Friedman*, 13 F. Supp. 2d at 56–57 (noting evidence that off-label use of calcium channel blockers deprived patients of more effective treatments).

In any event, a drug's safety for a second use is not established once a drug has been approved (and thus deemed safe and effective) for a first use. Rather, a drug that is safe for one use can be life threatening for another. For example, the drug bromocriptine is safe for use in treating certain diseases such as Parkinson's disease, but can cause stroke when used to suppress lactation in post-partum women. *See* 59 Fed. Reg. 43347 (1994) (FDA notice of withdrawal of approval for use to suppress lactation); FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017962s065s068lbl.pdf, at 4, 11 (current product labeling, listing approved uses and warning against use by lactating women).

Hormone replacement drugs provide another example. Throughout the 1990s, doctors prescribed hormone replacement drugs to women as a preventative measure against a range of illnesses, including heart disease, breast cancer, and Alzheimer's disease. G. Kolata and M. Petersen, *Hormone Replacement Study a Shock to the Medical System*, N.Y. Times, July 10, 2002, at A1. Although the FDA had approved hormone replacement drugs for treating specific symptoms associated with menopause, such as hot flashes, it had not approved the drugs for these other uses. *Id.* After millions of prescriptions had been written, a large government-funded study

found that use of the drugs actually *increased* women's risk of developing some of the very health problems the drugs were supposed to treat. *Id.*

Unfortunately, bromocriptine and hormone replacement drugs are just two of many examples. *See also*, *e.g.*, *Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678 (E.D. Pa. 2006) (Elidel approved as safe and effective to treat dermatitis, but poses risk of causing cancer when used off-label in patients less than two years old); *Friedman*, 13 F. Supp. 2d at 56–57 (noting off-label prescriptions of anti-arrythmic drugs encainide and flecainide to treat minor heart-rhythm disturbances in patients with recent heart attacks caused an estimated 3,000 to 10,000 patient deaths per year); *see generally* 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, 301–06 (2003) (detailing history of harms resulting from marketing of drugs for uses for which they had not been shown to be safe and effective).

Manufacturers' own assurances about what claims of safety and efficacy are well-supported are no substitute for requirements of FDA premarket approval based on evidence of safety and efficacy. Rather, extensive evidence shows that companies exploit marketing techniques to deceive doctors about the safety and effectiveness of off-label uses. For example, when selecting the educational material to send to doctors or to present at seminars, drug manufacturers choose material that plays up positive results and omits information about side-effects, adverse reactions, and warnings. Mark A. Ford, *Another Use of OxyContin: The Case for Enhancing Liability*

for Off-Label Drug Marketing, 83 B.U. L. Rev. 429, 434 (2003); *see also Friedman*, 13 F. Supp. 2d at 65 (noting that "manufacturers will likely only seek to disseminate information that presents their product in a favorable light"). Companies may also present doctors with the results of preliminary studies with small sample sizes when the results reflect favorably on their drugs, while ignoring even well-documented studies showing the opposite, negative result. *Friedman*, 13 F. Supp. 2d at 65. Doctors are thus "led to believe that a certain drug is safe and effective because a manufacturer has found, and aggressively promoted, 'the one' article that supports use of their drug, even if there exists considerable evidence to the contrary." *Id.*

These methods are particularly deceptive because drug studies are overwhelmingly funded by the drug companies themselves. Editorial, *Sponsorship, Authorship, and Accountability*, 345 New Eng. J. Med., Sept. 13, 2001, at 825. The studies thus often lack the objectivity on which reliable medical research is based. *Id.* Even worse, the inherent bias may be hidden by drug companies that hire ghostwriters or recruit academics to pose as authors. Joseph S. Ross, et al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, J. Am. Med. Ass'n, Apr. 16, 2008, at 1800–12. Merck, for example, funded a clinical study of Vioxx that appeared to test the safety of the drug but was actually designed and run by the company's marketing department to promote sales. Kevin P. Hill, et al., *The ADVANTAGE Seeding Trial: A Review of Internal Documents*, Annals of Internal Med., Aug. 19, 2008, at 251–58. Merck did not disclose to the study participants or the publishing journal that the study was a marketing exercise. *Id.* Similarly, Parke-

Davis designed and commissioned research to promote its drug Neurontin and devised a "publication strategy" that included contracts with medical-education companies to write articles on specified topics involving off-label use. *See* C. Seth Landefeld & Michael A. Steinman, *The Neurontin Legacy—Marketing through Misinformation and Manipulation*, 360 New Eng. J. Med., Jan. 8, 2009, at 103–06 (Parke-Davis engaged in 'the systematic use of deception and misinformation to create a biased evidence base and manipulate physicians' beliefs and prescribing behaviors.").

As the primary authors of studies, drug companies also have the ability to suppress unfavorable results. As one study found, drug companies selectively report the outcomes of clinical trials. S. Swaroop Vedula, et al., *Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use*, 361 New Eng. J. Med., Nov. 12, 2009, at 1963–71. Unsurprisingly, the studies drug companies choose not to publish overwhelmingly report negative or inconclusive results. Erick H. Turner, et al., *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 New Eng. J. Med., Jan. 17, 2008, at 252–60. In 2004, for example, Merck withdrew Vioxx from the market after revelations that the company had suppressed evidence that the drug caused an increased risk of heart attack and that the company had attempted to discredit or "neutralize" doctors who were critical of the drug. Cecily Walters, *Researchers Reveal Merck's Ghostwritten Vioxx Studies*, Trial, July 2008.

Although marketing drugs for unapproved uses thus poses considerable threats to public health and safety, the regulatory scheme strikes a balance by permitting manufacturers to discuss their drugs in scientific and academic literature and in public discourse. Drug companies are not prohibited from continuing to fund research, publishing their results, and generally engaging in public discussion about their drugs, so long as these forms of communication do not evince an intent to distribute their drugs for unapproved uses, which remains prohibited. FDA, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 2009), *available at* http://www.fda.gov/oc/op/goodreprint.html. As its actions in this case reflect, the FDA recognizes that "dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs" is sometimes appropriate. *Id.* Accordingly, the FDA allows drug companies to distribute reprints of journal articles and reference publications to doctors if the reprints are unbiased and scientifically valid. *Id.*

The FDA's current guidelines allow drug companies to engage in public discourse and scientific debate, while addressing the most common problems resulting from unregulated marketing of drugs for unapproved uses. For example, the guidelines address the problem of incomplete, skewed, or biased data by stating that reprints should be accompanied by a disclosure identifying any conflicts of interest, *id.*, and by limiting a manufacturer's distribution of publications funded by,

written at the request of, or influenced by the manufacturer. *Id.* They also include additional protections designed to insure that distributed information is scientifically sound, stating, for example, that reprints should address well-controlled studies and be published in a generally available, peer-reviewed journal. *Id.*

The relief sought by Amarin here would upset a careful balance reflecting Congress's decision that, to protect patients, a new drug may not be marketed with the intent that it be put to an unapproved use. As explained above, Amarin's theory would threaten the entire structure of drug regulation under the FDCA, which is premised on the requirement of premarket approval based on demonstration of a drug's safety and efficacy for each intended use.

CONCLUSION

The motion for a preliminary injunction should be denied.

Respectfully submitted,

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