UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PACIRA PHARMACEUTICALS, INC., et al., Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION, et al., Defendants.	Civil Action No. 15-cv-07055-RA

BRIEF OF *AMICUS CURIAE* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

CASES **Page(s)**

STATUTES AND REGULATIONS

OTHER AUTHORITIES

INTEREST OF *AMICUS CURIAE*

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's mission is to advocate public policies that encourage the discovery of life-saving and life-enhancing medicines. PhRMA's members are dedicated to discovering medicines that help patients lead longer, healthier, and more productive lives. In 2014 alone, PhRMA's members invested an estimated $51.2 billion in efforts to discover and develop new medicines. *See* PhRMA, 2015 Biopharmaceutical Research Industry Profile, at 36 fig.13 (2015), http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf. PhRMA frequently files *amicus curiae* briefs in cases raising matters of significance to its members.

PhRMA has a substantial interest in ensuring that pharmaceutical manufacturers can rely upon the indications set forth in the FDA-approved labeling of their products to delineate which educational communications FDA will not challenge as promoting an *un*approved use of the product. If FDA can effectively rescind or narrow its approval of a drug and invalidate truthful communications that track the language of the indications set forth in the drug's approved labeling, without notice or compliance with the requisite procedures, manufacturers will not know what they can and cannot say about their products. Not only would this arbitrary approach impede business planning; it would also violate the First Amendment right of pharmaceutical manufacturers to share truthful, non-misleading information about the medicines they research and develop.

Like Plaintiff Pacira Pharmaceuticals, Inc. ("Pacira"), PhRMA members plan their business and tailor their communications to healthcare professionals based on the FDA-approved labeling of their products. PhRMA members also operate under the same FDA regulations

identified in Pacira's Complaint. Pacira contends that FDA is now reading those regulations to ban truthful, non-misleading statements that are drawn from and consistent with a product's approved labeling, because, in FDA's view, those statements do not meet the FDCA's "substantial evidence" standard that governs the *approval* of medicines. Whatever the merits of that standard as a basis for approving a drug, it is not in all instances a measure of truth. Healthcare professionals need truthful, non-misleading information to help them decide which medicines are most appropriate for their patients. PhRMA members are a key source of such information, and they want to provide it. When FDA denies protection to the indications unambiguously set forth in a product's approved labeling, it chills that critically important speech and empowers arbitrary regulatory decision-making that impinges on First Amendment rights.

INTRODUCTION

PhRMA has long supported FDA's broad regulatory authority over the labeling of pharmaceutical products. Under the FDCA, FDA can properly determine what indications appear in a product's approved labeling. The Agency also can police whether a manufacturer's communications with healthcare professionals about its product are false or misleading. In particular, FDA can insist that the manufacturer not suggest uses for its products beyond what the scientific evidence supports. The FDA-approved labeling reflects the uses that FDA has determined have scientific support. To the extent, however, that FDA wishes to narrow a drug's labeling after having approved it and the product it accompanies, the Agency must adhere to the required regulatory process and provide the manufacturer with notice and an opportunity to comment.

This is particularly important in light of the First Amendment protections for communications by pharmaceutical companies to healthcare professionals about the companies' products. Therefore, the Court should insist that FDA's regulation of Pacira's communications about its medicine adhere meticulously to the governing statute, that FDA clearly articulate the relevant regulatory standards, and that it apply those standards consistently. Only in this way can the Court avoid the serious constitutional questions that, in a case like this one, would otherwise require resolution.

The Court should also bar FDA from using informal regulatory tools to threaten enforcement action against manufacturers for making truthful, non-misleading statements about approved drugs for the sole reason that they are not supported by FDA's interpretation of "substantial evidence." Those threats significantly and improperly chill a wide swath of valuable First Amendment-protected speech. The substantial evidence standard governs whether FDA should approve a drug, not whether communications about the drug are truthful. Falling short of that standard, as FDA defines it, does not automatically render the manufacturer's communications false or misleading. Controlling case law establishes that FDA may not pursue enforcement against a manufacturer for truthful communications with healthcare professionals, provided the manufacturer includes adequate disclosures to enable the recipient of the communication to make a fully informed decision about using the product.

ARGUMENT

FDA's threats of enforcement action target two categories of truthful and non-misleading communications that Pacira wishes to make to well-educated healthcare professionals about its FDA-approved drug, EXPAREL: (1) statements about EXPAREL's effectiveness to control post-surgical pain in various surgical sites, not limited to the two specific sites studied in the

drug's pivotal trials, and (2) statements about EXPAREL's ability to control post-surgical pain for up to 72 hours. On the first category, FDA has no legitimate basis to restrict Pacira's speech because the Agency in fact *approved* EXPAREL for use in *all* surgical sites *without limitation*, as reflected in the Indications and Usage section of the drug's approved labeling. FDA's attempt to narrow EXPAREL's approval through an informal warning letter exceeds the Agency's authority, in an area where the limits on that authority are of constitutional import. Nor is the lack of "substantial evidence"—generally meaning, in FDA's view, two adequate and well-controlled clinical trials—alone a sufficient basis to restrict the second category of speech, addressing the duration of the relief that EXPAREL may provide. Pacira contends that one of the drug's pivotal trials supports the company's statement. That there is only one adequate and well-controlled clinical trial supporting the statement, instead of the two generally required under the "substantial evidence" standard, does not mean that the statement is untrue or misleading. It simply means that there is one adequate and well-controlled clinical trial instead of two. If the manufacturer appropriately discloses that fact and others necessary for healthcare professionals to evaluate the statement, the communications drawn from the pivotal trial may be truthful and non-misleading, despite the lack of a second trial. The substantial evidence standard is not and cannot be the sole measure of what is true and non-misleading.

I. FDA Cannot Use Threats of Enforcement to Narrow a Drug's Approved Uses Without Following the Statutory Procedures to Change a Drug's Labeling.

Pacira seeks to communicate with healthcare professionals about the use of its approved drug, EXPAREL, to control post-surgical pain in the context of various surgeries. *See* Compl. ¶¶ 6, 16, 19. According to the Complaint, FDA has threatened enforcement action against Pacira on the theory that EXPAREL is not approved to control post-surgical pain outside of the two specific surgeries at issue in the clinical trials that led to the approval. *Id.* ¶ 7. In FDA's

view, no matter what disclaimers Pacira provides, communicating with healthcare professionals about using EXPAREL after any other surgery would violate the FDCA. *Id.* ¶¶ 8-9; *see also id.* ¶¶ 15-17 (FDA reportedly withdrew its threat of enforcement solely because Pacira had ceased such communications). On its face, however, the "Prescribing Information" in EXPAREL's approved labeling covers post-surgical pain relief for *all* surgeries, not just two specific operations. *Id.* ¶ 4. It says, without limitation, that the drug is "indicated for administration into the surgical site to produce postsurgical analgesia." *Id.*

Pharmaceutical manufacturers must be able to rely on the FDA-reviewed and approved description of uses in a drug's labeling as reflecting FDA's determination that the drug is safe and effective for that use. The approved labeling is the fruit of a long process in which the Agency carefully considers the clinical data submitted by the sponsor of the new drug application. As part of that review, FDA's experts conduct extensive discussions with the manufacturer about the data. FDA may request additional clinical research, or may convene an advisory committee of experts to evaluate the application. The result of this arduous, comprehensive, and deliberative process is approval of the product for use as stated in the label (unless, of course, the application is rejected or additional research is required). During the pre-approval stage, FDA has ample opportunity to narrow or refine the approved indication and usage of a product to reflect the Agency's evaluation of the data.

It is a "long-settled principle" of administrative law—not to mention common sense and fairness—"that the rules promulgated by a federal agency, which regulate the rights and interests of others, are controlling upon the agency." *Montilla v. I.N.S.*, 926 F.2d 162, 166 (2d Cir. 1991) (citing *Columbia Broadcasting System, Inc. v. United States*, 316 U.S. 407 (1942); *United States ex rel. Accardi v. Shaughnessy*, 347 U.S. 260 (1954)). FDA's regulations make clear that a

drug's approved labeling is intended to provide certainty to readers regarding the Agency's reasoned determination that the drug is "safe and effective" for the stated indications. Indeed, FDA is required to specify in the labeling any "limitations" on, or "conditions" to, its approval. 21 C.F.R. § 201.57(a)(6), (c)(2). As set forth in a declaration supporting Pacira's motion for preliminary injunction, FDA has adhered to these requirements in the approved labeling of other post-surgical pain medications, including SUFENTA, DEPODUR, and VICOPROFEN. For those drugs, the Agency explicitly limited the approved indication in the drugs' labeling to specific types or locations of surgical sites. *See* Goldkind Decl. ¶ 47. There is no reason to believe FDA followed a different approach when it approved the broad indication for EXPAREL.

Manufacturers should not have to guess whether FDA may announce, potentially years later, that its approval of a drug was actually for a much narrower indication than the labeling explicitly states. Given the extensive review undertaken before product approval, any concerns FDA might have about the appropriate limitations in the Indications and Usage section should be addressed prior to approval. FDA's warning letter to Pacira relies on *other* parts of EXPAREL's approved labeling—the "Clinical Studies" and "Dosage and Administration" sections—that make reference to the two specific surgeries studied in the drug's pivotal trials. But, under FDA regulations, it is the "Indications and Usage" section of the labeling that "must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition . . . ." 21 C.F.R. § 201.57(c)(2). Companies must be able to rely on the FDA-approved language in this section regarding the approved indications and usage of the drug. No one should have to speculate whether FDA may later construe references to a drug's clinical trials in other sections as limiting the drug's approved indications.

Where an agency's action, such as FDA's approval of a drug and its accompanying labeling specifying the approved indication, "is based upon a defined procedure, even though generous beyond the requirements that bind such agency, that procedure must be scrupulously observed." *Vitarelli v. Seaton*, 359 U.S. 535, 539-40 (1959); *accord Morton v. Ruiz*, 415 U.S. 199, 235 (1974) (declining to address constitutional issues because case disposed of on this statutory ground). FDA's duty to "scrupulously observe" its procedures in this context is crucial, because pharmaceutical manufacturers, healthcare professionals, and patients alike rely on the drug's approved labeling in making medical judgments. Manufacturers in particular rely on it in determining what they can say about their medicines. *See Montilla*, 926 F.2d 162, 167 (2d Cir. 1991) (the duty "has continued vitality, particularly where a petitioner's rights are 'affected'" (quoting *Morton*, 415 U.S. at 235)).

If FDA's objective here was to rescind or otherwise narrow its unequivocally broad approval for EXPAREL to control pain in any and all surgical sites, the Agency should have followed the requisite procedure for doing so. Once FDA approves a new drug and its accompanying labeling, the FDCA and FDA's implementing regulations establish a rigorous process by which FDA can seek to amend the approved labeling. That procedure incorporates—as it must—the due process requirements of notice to the manufacturer and an opportunity for a hearing. *See* 21 U.S.C. §§ 355(o)(4), 355(e); 21 C.F.R. § 314.150(b)(3). Here, however, FDA has not even initiated, much less completed, that process. Instead, according to Pacira's Complaint, FDA informed Pacira of the Agency's interpretation of EXPAREL's labeling through a warning letter threatening that its speech about the drug's use in specific surgical sites other those in the pivotal studies constituted a criminal violation of the FDCA. Compl. ¶ 9. Neither the FDCA nor the Constitution allow FDA to use such threats, without any notice, to re-

interpret, rewrite, and substantially narrow the approved label of a drug—here, EXPAREL's approval to control post-surgical pain without regard to the type of surgery. *See Montilla*, 926 F.2d at 167 (the *Accardi* doctrine, requiring agencies to follow their own prescribed procedures, "is premised on fundamental notions of fair play underlying the concept of due process").

Additionally, FDA's extra-statutory self-help in the form of a warning letter, to restrict EXPAREL's approval retroactively chills free speech and thereby raises serious constitutional concerns. Indeed, if permitted, FDA's "regulation through warning letter" approach could deter manufacturers from speech that is entirely consistent with the label, lest FDA subsequently re-interpret the label and deem the speech inconsistent with the Agency's new gloss on the scope of the product approval. This capricious approach presents both a due process and a First Amendment problem. The Supreme Court has held that a law is impermissibly vague — and therefore violates due process — when it leaves room for a government enforcer to act in an arbitrary or discriminatory way. *F.C.C. v. Fox Television Stations, Inc.*, 132 S. Ct. 2307 (2012). Allowing FDA to jettison the statutory and regulatory procedures for amending a drug's approved labeling would invite such arbitrary decision-making by the Agency, as demonstrated in this case. The Court in *F.C.C. v. Fox* explained that arbitrary decision-making is especially troublesome in the context of First Amendment-protected speech because, by blurring the boundaries for permitted versus prohibited speech, it has a chilling effect on speakers. *Id*; *see also United States v. Williams*, 553 U.S. 285, 292 (2008); *Reno v. Am. Civil Liberties Union*, 521 U.S. 844, 871-72 (1997); *City of Lakewood v. Plain Dealer Pub. Co.*, 486 U.S. 750, 758 (1988) (invalidating a statute that granted too much discretion over speech-related activity because "*post hoc* rationalizations by the licensing official and the use of shifting or illegitimate criteria are far too easy, making it difficult for courts to determine in any particular case whether the licensor is

permitting favorable, and suppressing unfavorable, expression"); *Saia v. People of State of New York*, 334 U.S. 558, 562 (1948) (granting the government "uncontrolled discretion" to restrict speech "sanctions a device for suppression of free communication of ideas").

In this case, FDA's decision to approve EXPAREL and its accompanying labeling should have permitted Pacira to speak to healthcare professionals, without fear of reprisal, about the indications in the approved labeling. If companies can no longer rely on the plain text of a drug's approved labeling to determine what uses FDA approved, then it could be too risky to speak. First Amendment and due process principles preclude such censorship.

The Court should avoid the constitutional questions raised by FDA's approach. *See Edward J. DeBartolo Corp. v. Florida Gulf Coast Bldg. & Const. Trades Council*, 485 U.S. 568, 575 (1988) (court should assume Congress did not intend a statutory meaning that raises constitutional problems); *Solid Waste Agency of N. Cook Cnty. v. U.S. Army Corps of Engineers*, 531 U.S. 159, 172 (2001) (same principle applies to avoid constitutional questions that would arise from agency interpretations of authorizing statutes). To that end, PhRMA urges the Court to require that FDA abide by the plain language of the label and treat any communications about the use of EXPAREL to control post-surgical pain in contexts other than the two surgeries studied in the clinical trials as consistent with the drug's *approved* use. Moreover, because Pacira seeks to communicate with sophisticated healthcare professionals about an approved use, the only remaining issue under controlling Supreme Court and Second Circuit precedents is whether Pacira proposes to provide enough information and substantiation to render the company's speech truthful and non-misleading.

In this regard, the Supreme Court's decision in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), makes clear that the dispositive inquiry is whether the communication is truthful

and non-misleading, not whether it is "promotional" or "scientific." There, the Supreme Court specifically affirmed the value of pharmaceutical communications, promotional or otherwise, noting that "[t]he defect in Vermont's law is made clear by the fact that many listeners find detailing instructive." *Id.* at 2671. So too here: Pacira's speech about the approved use of EXPAREL in various surgical sites is instructive to doctors. FDA cannot restrict that speech unless it is false or misleading in that context. *See also United States v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012) (holding that to punish drug manufacturer's truthful, non-misleading speech "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information could inhibit, to the public's detriment, informed and intelligent treatment decisions"); *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, No. 15-civ-3588-PAE, 2015 WL 4720039, at *26-*27 (S.D.N.Y. Aug. 7, 2015) (explaining that any justification for punishing a drug manufacturer's speech is missing the *actus reus* requirement where that speech is truthful and non-misleading).

The First Amendment also bars FDA from censoring a pharmaceutical manufacturer's speech if there is a less restrictive way to directly advance substantial governmental interests. *See, e.g.*, *Caronia*, 703 F.3d at 168 ("[t]he government's interests could be served equally well by more limited and targeted restrictions on speech"). FDA's interest is to ensure that physicians receive truthful, non-misleading information to permit them to make appropriate prescribing decisions. FDA could accomplish that objective by requiring Pacira to disclose to physicians that EXPAREL was tested only for the two surgeries discussed in the clinical trials section of the drug's Prescribing Information, and to require as well that Pacira disclose any differences in dosing or other information particular to another surgery, plus any contrary studies. Before

barring or chilling speech, it is FDA's burden to show at the very least why these steps would not be adequate. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 373 (2002).

II. FDA's "Substantial Evidence" Standard Is Not the Measure of Truthful and Non-Misleading Communications with Healthcare Professionals.

Pacira also challenges FDA's ability to restrict the company's speech on the sole ground that it fails the Agency's regulatory "substantial evidence" standard for efficacy and comparative claims. *See* 21 C.F.R. § 202.1(e)(6)(i). Indeed, whether a statement is truthful and non-misleading depends on whether it is true and does not mislead, not on whether it satisfies some evidentiary threshold chosen by FDA. To the extent FDA objects to Pacira's 72-hour claim on the ground that it does not meet the Agency's "substantial evidence" standard, the regulation imposes an unnecessary and impermissible burden on speech that in fact may be truthful and non-misleading.

According to the Complaint, Pacira wishes to inform healthcare professionals of EXPAREL's ability to control post-surgical pain for up to 72 hours — a claim that Pacira contends is supported by the drug's pivotal trial. *See* Compl. ¶¶ 14, 16, 19. If FDA contends that Pacira's proposed speech is "false or misleading" solely because only one adequate and well-controlled clinical trial supports the claim — whereas FDA's substantial evidence standard generally requires two such trials to support an efficacy claim — the Agency's characterization of "false or misleading" speech in this context would be vastly overbroad and misguided. Contrary to that view, speech about a scientific claim can be truthful and non-misleading even absent two supporting clinical trials, particularly if the speaker makes sufficient disclosures about the empirical support for the communication. So long as the empirical support actually substantiates the statement that EXPAREL is effective for up to 72 hours, and Pacira makes

appropriate disclosures regarding any limits on the clinical data and contrary evidence, the statement would not be false or misleading.

Although FDA has statutory authority to apply a heightened evidentiary standard for approving new drugs for commercial marketing, that does not authorize FDA to deem a truthful statement about an approved drug false, or to treat a fully supported contextual statement as misleading, based on the amount of clinical evidence the Agency prefers. Courts in fact have rejected the notion that FDA's standards for drug approval are the yardstick for determining whether claims about a drug are truthful and non-misleading. In *Caronia*, for instance, the Second Circuit held that speech about unapproved uses of a drug can be truthful and non-misleading. 703 F.3d at 149. In *Amarin*, this Court recently held that principle applicable to the unapproved use of a drug that was supported by only one adequate and well-controlled clinical trial. 2015 WL 4720039, at *9. Likewise, the U.S. District Court for the District of Columbia has held that health claims are not "inherently misleading" simply because FDA had not yet approved them. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998).

Similarly, the D.C. Circuit has specifically rejected the notion that two adequate and well-controlled clinical trials are uniformly necessary to make an efficacy claim non-misleading in the context of food advertising about health benefits. *See POM Wonderful, LLC v. F.T.C.*, 777 F.3d 478 (D.C. Cir. 2015). In rejecting an FTC remedial order that would have imposed such a prospective requirement, the court of appeals explained that the order failed *Central Hudson*'s requirement that a restriction on commercial speech "directly advance[] the governmental interest":

> [T]he Commission fails adequately to justify a categorical floor of two [randomized and controlled human clinical trials] for any and

> all disease claims. It of course is true that, all else being equal, two RCTs would provide more reliable scientific evidence than one RCT, affording added assurance against misleading claims. It is equally true that three RCTs would provide more certainty than two, and four would yield more certainty still. But the Commission understandably does not claim a myopic interest in pursuing scientific certitude to the exclusion of all else, regardless of the consequences.

Id. at 502. Here, too, manufacturers' speech has benefits that preclude application of such a prior restraint. As the Second Circuit held in *Caronia*, "barriers to information could inhibit, to the public's detriment, informed and intelligent treatment decisions." 703 F.3d at 166.

For purposes of the First Amendment, the question whether a particular claim about an approved drug is truthful and non-misleading should not turn automatically on FDA's definition of "substantive evidence" alone, but rather on multiple factors, including: (a) the accuracy of the statement; (b) the level of disclosure made to ensure the listener is adequately informed of material facts; and (c) the degree of sophistication of the listener. *Cf. Sorrell*, 131 S. Ct. at 2670-71 ("The fear that people would make bad decisions if given truthful information cannot justify content-based burdens on speech," especially "when the audience, in this case prescribing physicians, consists of sophisticated and experienced consumers." (quotation marks omitted)); *Thompson*, 535 U.S. 357, 374 (2002) (calling it a "questionable assumption" that doctors would not play a gatekeeping function and rejecting, in any event, the notion "that people would make bad decisions if given truthful information about compounded drugs"). In *Caronia*, the Second Circuit explained that "if the government is concerned that off-label promotion may mislead physicians" it could develop guidance about what statements tend to mislead doctors or could "develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs." 703 F.3d at 168.

Under these principles, as long as the efficacy claim is consistent with the available evidence and the manufacturer adequately discloses the basis for the claim as well as contradictory evidence, the communications would be truthful and non-misleading even if supported by less than two adequate and well-controlled clinical trials. For instance, a manufacturer may state truthfully that an efficacy or comparative claim rests on one adequate and well-controlled clinical trial, so long as the manufacturer also makes any other disclosures necessary for healthcare professionals to evaluate the merits of the claim, including studies that may contradict the claim. The same would hold for communications based on other forms of scientific evidence, such as a retrospective analysis of data from a clinical trial or of a sub-group from a clinical trial. Even though such information may not fulfill FDA's vision of "substantial evidence," with appropriate disclosure of the limitations on the data, the information could be truthful and non-misleading and could have educational value to a healthcare professional.

Accordingly, as long as the pivotal study supports Pacira's 72-hour claim, and the company adequately discloses the basis for the claim and provides other contextual information to ensure the speech is not misleading, the company's proposed communications with healthcare professionals would be truthful and non-misleading. The First Amendment does not permit FDA to ban such communications based solely on the lack of two supporting adequate and well-controlled clinical trials.

CONCLUSION

The Court should require FDA to adhere to its own rules and prevent FDA from determining that a manufacturer's claims are false and misleading based on any standard other than their truthfulness and transparency. The Court therefore should grant Pacira's motion for preliminary injunction.

Dated: October 15, 2015

Respectfully Submitted,

ARNOLD & PORTER LLP

By: s/ Craig A. Stewart

Craig A. Stewart
399 Park Avenue
New York, New York 10022
(212) 715-1000 (Tel)
(212) 715-1399 (Fax)
Craig.Stewart@aporter.com

Robert N. Weiner
Jeffrey L. Handwerker
R. Stanton Jones
Taylor M. Owings
601 Massachusetts Ave., NW
Washington, DC 20001-3743

Counsel for
Pharmaceutical Research and Manufacturers of America (PhRMA)