UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 14-11689-RWZ

ZOGENIX, INC.

v.

DEVAL PATRICK, in his official capacity as GOVERNOR OF MASSACHUSETTS, *et al.*

MEMORANDUM OF DECISION

July 8, 2014

ZOBEL, D.J.

The issue is whether two Massachusetts regulations limiting the prescribing and handling of Zohydro™ ER ("Zohydro"), a Food and Drug Administration-approved opioid analgesic, frustrate federal statutory objectives in violation of the Supremacy Clause of the United States Constitution. Plaintiff Zogenix, Inc., believes they do and moves for a preliminary injunction barring their enforcement (Docket # 46). Defendants, Commonwealth health officials sued in their official capacities, believe they do not and move to dismiss (Docket # 44). Plaintiff's motion is ALLOWED IN PART and DENIED IN PART. Defendants' motion is DENIED.

I. Background[1]

On October 25, 2013, the Food and Drug Administration ("FDA") approved

[1] I take the basic, undisputed facts from the Verified Second Amended Complaint (Docket # 51).

Zohydro, the only opioid analgesic whose sole active ingredient is hydrocodone. Unlike other hydrocodone analgesics, Zohydro does not contain acetaminophen, which may cause liver damage. As an "extended release" medication, Zohydro dispenses pain relief over a twelve-hour period. The drug, however, lacks an "abuse resistant formulation," permitting individuals to crush the pills, inhale or inject them, and immediately experience the full effect. Some Massachusetts officials worried that Zohydro could cause or worsen opioid abuse in the Commonwealth.

Governor Patrick authorized, and the Department of Public Health ("DPH") issued, an emergency order which banned the prescribing, ordering, dispensing, or administration of Zohydro. Plaintiff sued and sought a preliminary injunction on the ground that federal law preempted the emergency order. I agreed, and on April 15, 2014, enjoined enforcement of DPH's emergency order. I stayed the preliminary injunction until April 22, 2014.

On that day, the Board of Registration in Medicine ("BORIM") promulgated an emergency regulation requiring an individually licensed prescriber to do the following before prescribing Zohydro[2]:

> (a) Thoroughly assess the patient, including an evaluation of the patient's risk factors, substance abuse history, presenting conditions(s), current medication(s), and a check of the online Prescription Monitoring Program;
>
> (b) Discuss the risks and benefits of the medication with the patient;
>
> (c) Enter into a Pain Management Treatment Agreement with the patient

[2]The Massachusetts regulations at issue do not refer to Zohydro by name, but instead to "a hydrocodone-only extended release medication that is not in an abuse deterrent form." Docket # 51-4. Zohydro is the only such drug.

> that shall appropriately address drug screening, pill counts, safe storage and disposal and other requirements based on the patient's diagnoses, treatment plan, and risk assessment;
>
> (d) Supply a Letter of Medical Necessity as required by the Board of Registration in Pharmacy that includes the patient's diagnoses and treatment plan, *verifies that other pain management treatments have failed*, indicates that a risk assessment was performed and that the licensee and the patient have entered into a Pain Management Treatment Agreement; and
>
> (e) Document 243 CMR 2.07(25)(a)-(d) in the patient's medical record.

243 CMR 2.07(25) (emphasis added).

On May 6, 2014, the Board of Registration in Pharmacy ("BORIP") promulgated two Zohydro-related regulations. The first states that "[a] certified pharmacy technician, pharmacy technician, pharmacy technician trainee, or pharmacy intern may not handle [Zohydro]." 247 CMR 8.05(3). The second contains a host of prerequisites a pharmacist must satisfy before dispensing Zohydro, including: (1) storing Zohydro in a locked cabinet; (2) dispensing Zohydro in a container with a child-proof safety cap; (3) reviewing the Letter of Medical Necessity; (4) including a warning about Zohydro's dangers; (5) providing counseling on various issues; and (6) checking the patient's history on the Prescription Monitoring Program. Id. 9.04(8).

On May 8, 2014, the Board of Registration of Physicians Assistants ("BOROPA") promulgated a set of regulations identical to the ones BORIM passed. 263 CMR 5.07(12).

II. Legal Standard

A. Preliminary Injunction

To obtain a preliminary injunction, Zogenix must establish that (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary injunctive relief; (3) the balance of equities weighs in its favor; and (4) an injunction is in the public interest. Winter v. Natural Res. Def. Council, 555 U.S. 7, 20 (2008).

B. Motion to Dismiss

A complaint must contain a "short and plain statement of the claim showing that the pleader is entitled to relief." Fed. R. Civ. P. 8(a)(2). The court accepts as true all factual allegations contained in the complaint, but not legal conclusions. Ashcroft v. Iqbal, 556 U.S. 662, 678 (2009). If the complaint fails to state a plausible claim upon which relief can be granted, it must be dismissed. Id.

III. Analysis

Zogenix challenges the Commonwealth regulations which require that (1) doctors or physician assistants certify in the Letter of Medical Necessity ("LMN") that "other pain management treatments have failed," see 243 CMR 2.07(25)(d) (BORIM), 263 CMR 5.07(12)(d) (BOROPA); and (2) only pharmacists may handle Zohydro, see 247 CMR 8.05(3). Its main claim is that federal law preempts these regulations.[3]

[3]Zogenix also contends that the regulations violate the Equal Protection Clause because they single out Zohydro from other extended-release/long-acting opioid medications on the market without a rational basis for doing so. Sec. Am. Compl. ¶¶ 82-83; see Village of Willowbrook v. Olech, 528 U.S. 562, 565 (2000) (stating elements for class-of-one Equal Protection claim). That argument is misplaced. The Supreme Court has held that forms of state action which involve "discretionary decisionmaking based on a vast array of subjective, individualized assessments" are ill-suited for class-of-one Equal Protection claims. Engquist v. Or. Dep't of Agric., 553 U.S. 591, 603 (2008). Class-of-one claims instead involve "legislative or regulatory classifications in which there is "a clear standard against which departures, even for a single plaintiff, [can] be readily assessed." Id. at 602. Zogenix does not explain how the challenged regulations were compelled by legislative classification rather than a discretionary assessment of Zohydro's risks. It thus has not established that a class-of-one Equal Protection claim is

The Supremacy Clause gives Congress the power to preempt state law. U.S. Const. art. VI cl. 2. There are different types of preemption. At issue here is "obstacle preemption," which occurs when, "under the circumstances of [the] particular case, [the challenged state law] stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." Hines v. Davidowitz, 312 U.S. 52, 67 (1941). "What is a sufficient obstacle is a matter of judgment, to be informed by examining the federal statute as a whole and identifying its purpose and intended effects." Crosby v. Nat'l Foreign Trade Council, 530 U.S. 363, 373 (2000). The Supreme Court put it this way more than one hundred years ago: "If the purpose of the [federal] act cannot otherwise be accomplished-if its operation within its chosen field else must be frustrated and its provisions be refused their natural effect-the state law must yield to the regulation of Congress within the sphere of its delegated power." Savage v. Jones, 225 U.S. 501, 533 (1912).

The Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-399f, sets forth the pertinent federal purposes and objectives. The FDCA created the FDA and required it to "protect the public health" by ensuring that "drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). The FDA must approve new drugs before they are introduced to the market. Id. § 355(a). To do so it employs "a structured risk-benefit assessment framework." Id. § 355(d)(7). It will not approve a new drug if it concludes the drug is unsafe, or if there is insufficient information from which to determine

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an appropriate cause of action. I also do not consider Zogenix's undeveloped arguments that the Commonwealth's regulations violate the Contract Clause and the Commerce Clause of the United States Constitution (Counts III and IV). See U.S. Const. art. I § X cl. 1; id. art. I § VIII cl. 3.

whether the drug is safe. 21 C.F.R. § 314.125(b)(3)-(4). But if a new drug passes the benefit-risk assessment, the FDA "promote[s] the public health" by making it available to the public. 21 U.S.C. § 393(b)(1).

The essence of plaintiff's preemption argument is that defendants are trying to make scarce or altogether unavailable a drug that the FDA, by approving it, has said should be available. First, they contend the regulations amount to a *de facto* ban on Zohydro. The LMN requirement that "other pain management treatments have failed" requires a physician to cycle a patient through unnecessary and possibly dangerous pain management alternatives before prescribing Zohydro. And the "pharmacist-only" regulation is incompatible with the staffing structure of many pharmacies, making it impracticable for pharmacies to carry Zohydro. If physicians cannot readily prescribe Zohdryo and pharmacies will not stock it, then Zohydro is not, as the FDA required, available to the public. Second, it claims that federal law preempts the regulations even if they do not functionally ban Zohydro. The FDA approved Zohydro for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Docket # 49-1 at 29. The alternative treatment options must only be inadequate; they need not have been tried and failed, as the Commonwealth's regulation requires. The regulation thus undermines the FDA's power to approve drugs for specific uses and purposes.

Defendants see it differently. The "LMN regulation" does not refer to any particular treatments that must fail. The regulation does not require physicians to prescribe other opioids or subject patients to medically ill-advised treatments before

prescribing Zohydro. Mem. in Supp. of Mot. to Dismiss, Docket # 45, at 12 n.12. The regulation gives physicians far more flexibility than plaintiff is willing to admit. Zohydro will thus remain available, and the regulations are permissible. Furthermore, state governments have primary authority to regulate health and safety, including the practice of medical professionals. The FDA itself has recognized that it "does not generally regulate the practice of pharmacy or the practice of medicine -- the States traditionally have regulated both the prescribing and dispensing of drugs." Hearing Before the Subcomm. on Oversight & Investigations of the House Comm. on Commerce, 106th Cong. 99 (1999) (statement of Janet Woodock, M.D., Director of the FDA Center for Drug Evaluation & Research). Defendants are not treading on federal ground, they say, but are merely regulating within the proper scope of their constitutional authority.

Sure enough, the Commonweath's police powers permit it to regulate the administration of drugs by the health professions. Gonzales v. Oregon, 546 U.S. 243, 270-71 (2006); Whalen v. Roe, 429 U.S. 589, 603 (1977). But it may not exercise those powers in a way that is inconsistent with federal law. Preemption principles have no less heft because health is a matter of "special concern" to the states. Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta, 458 U.S. 141, 153 (1982) (concluding as much with respect to real property law); see Free v. Bland, 369 U.S. 663, 666 (1962) ("The relative importance to the State of its own law is not material when there is a conflict with a valid federal law, for the Framers of our Constitution provided that the federal law must prevail."); Gibbons v. Ogden, 22 U.S. (9 Wheat.) 1, 210 (1824) (state laws

passed pursuant to police powers must yield if they conflict with federal law). To say, as defendants do, that they are exercising their constitutional authority does not answer the question. I must do as Savage instructs and assess whether the regulations prevent the accomplishment of the FDCA's objective that safe and effective drugs be available to the public.

By any reckoning, the text of the "LMN regulation" is ambiguous. Exactly what "pain management treatments" must fail before a doctor may prescribe Zohydro? Plaintiff believes other opioids must fail. Defendants do not believe a physician must prescribe other opioids before she may prescribe Zohydro. One need look no further than defendants' own affiant to doubt their position. The affidavit of Dr. Jane Liebschutz, Associate Chief of General Internal Medicine at Boston Medical Center, states the following:

- "[B]efore a provider could appropriately prescribe Zohydro™ ER, there would have to be a series of conditions met. First and foremost, the patient would have to have tried multiple non-opioid medications." Docket # 56-5 ¶ 2.

- "I would not prescribe Zohydro™ ER to a patient who had not been on daily short-acting opioids for at least 12 weeks. In my professional opinion, Zohydro™ ER is only suitable for patients who are already opioid tolerant[.]" Id. ¶ 3.

- "In my professional opinion, Zohydro™ ER would be a *last-resort opioid* because there are safer and more effective options for treating pain such as long acting morphine, and long-acting oxycodone with abuse-deterrent formulation (e.g. Oxycontin™). Id. ¶ 7 (emphasis added).

Of course, this may be one doctor's opinion. But if the Commonwealth interprets its regulation to make Zohydro a last-resort opioid, it undeniably makes Zohydro less

available. That presents a constitutional problem.

The "LMN regulation" is unclear in another way. How long ago must the "other pain management treatments" have failed? As a Schedule II drug, Zohydro prescriptions are subject to a thirty-day maximum. Sec. Am. Compl., Docket # 51, ¶ 48. Must a physician try a new treatment—or, because it is plural in the regulation, *treatments*—before writing each new prescription, or may she rely upon a failed treatment in the more distant past? If she may, how distant? For example, if a physician had prescribed a different opioid six months ago with no success, could she write a prescription for Zohydro and still comply with the "LMN regulation?" Could a fellow physician rely on a failed regimen of vitamins and acupuncture two months ago? What, indeed, does "failure" mean in this context? The regulation has no response to these rather obvious contingencies. If the Commonwealth interpreted its regulation to require a fresh failure as a precondition to each 30-day Zohydro prescription, it would severely frustrate Zohydro's availability and pose significant constitutional concerns.

As for the "pharmacist-only regulation," the parties rely on competing affidavits. In a sealed declaration, Zogenix co-founder and Chief Executive Officer Roger L. Hawley discloses that unspecified major retail pharmacy chains do not plan to stock Zohydro because the "pharmacist-only regulation" is "fundamentally incompatible with personnel infrastructure and established policies for dispensing ER/LA opioids." Declaration of Roger L. Hawley ¶ 3. Defendants present the affidavit of Michael Reppucci, R. Ph., owner of and pharmacist at Inman Pharmacy in Cambridge, Massachusetts. Docket # 56-6. Reppucci states that because BORIP already regulates

pharmacy technicians, "prohibiting any pharmacy technicians from transporting and handling Zohydro does not add any substantial administrative burden or present substantial logistical problems." Id. ¶ 6. Neither party directs the court to any pharmacy's announcement that it will or will not carry Zohydro.

What is the proper remedy given such uncertainty? Defendants may interpret and enforce the challenged regulations in a way that obstructs the FDCA's objectives. At present, however, given the lack of a record of enforcement, it is unclear whether such an obstacle exists. The Supreme Court has reminded lower courts that they should not find preemption where there is no clearly discernible conflict between state and federal law. See Geier v. Am. Honda Motor Co., 529 U.S. 861, 866 (2000); Huron Portland Cement Co. v. City of Detroit, 362 U.S. 440, 446 (1960). At the same time, plaintiff should not bear the brunt of the defendants' vague regulations, waiting for an adequate record of enforcement to develop while the clock ticks on its three-year exclusivity period. See 21 U.S.C. §§ 355(c)(3)(E); (j)(5)(F). And of course, defendants may not use vague regulations to sidestep or countermand federal law.

With these principles in mind, I conclude as follows:

- Plaintiff has stated a plausible claim for relief. Defendants' motion to dismiss is denied without prejudice.[4]

- Plaintiff's motion to preliminarily enjoin the "LMN regulation," 243 CMR 2.07(25)(d) and 263 CMR 5.07(12)(d), is allowed. If defendants provide adequate and constitutional guidance to physicians regarding the prerequisites for prescribing Zohydro in compliance with the regulation, then they may thereafter move to lift the injunction.

[4]Defendants also move to dismiss on standing grounds, but they failed to develop this argument in their memorandum in support of their motion to dismiss. It is therefore waived.

- Because its sealed declaration does not provide sufficient detail that pharmacies will not carry Zohydro, plaintiff has not met its burden of proof on the "pharmacist-only regulation," 247 CMR 8.05(3). Its motion for a preliminary injunction is denied without prejudice to renewal upon a more detailed submission.

IV. Conclusion

Plaintiff's motion for a preliminary injunction (Docket # 46) is ALLOWED IN PART and DENIED IN PART without prejudice. Defendants' motion to dismiss (Docket # 44) is DENIED without prejudice.

July 8, 2014 /s/Rya W. Zobel

DATE RYA W. ZOBEL
UNITED STATES DISTRICT JUDGE