IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ZOGENIX, INC. and ZOGENIX INTERNATIONAL LTD., Plaintiffs, v. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No. 21-1252-RGA (Consolidated)

MEMORANDUM

Before me is the Report & Recommendation of a United States Magistrate Judge. (D.I. 154).[1] The Report addresses the following motions: (1) Defendants' motion to dismiss the complaint for lack of subject matter jurisdiction and failure to state a claim under Federal Rules of Civil Procedure 12(b)(1) and 12(b)(6), respectively (C.A. No. 22-1232-RGA, D.I. 14); and (2) Plaintiffs' motion to amend the complaint under Federal Rule of Civil Procedure 15(a). (D.I. 95). The Report recommends that I deny Defendants' motion to dismiss under Rule 12(b)(1), grant Defendants' motion to dismiss under Rule 12(b)(6), and grant-in-part Plaintiffs' motion to amend under Rule 15(a). (D.I. 154 at 1–2). Plaintiffs filed objections to the Report. (D.I. 165). Defendants responded to Plaintiffs' objections. (D.I. 172).

I will adopt the factual findings and legal conclusions in the Report. I do not separately recite any of the facts except as I see necessary to explain my decision.

[1] Unless otherwise indicated, docket citations are to the docket in No. 21-1252.

I. LEGAL STANDARDS

Magistrate Judges have the authority to make recommendations as to the appropriate resolution of a motion to dismiss pursuant to 28 U.S.C. § 636(b)(1)(B). The Court conducts a *de novo* review when determining whether to adopt a Magistrate Judge's report and recommendation on a dispositive motion. FED. R. CIV. P. 72(b)(3). For non-dispositive motions, such as a motion for leave to amend, the Court reviews findings of fact for clear error and conclusions of law *de novo*. *Cornell Univ. v. Illumina, Inc.*, 2017 WL 89165, at *8 (D. Del. Jan. 10, 2017). Upon review, the Court may accept, reject, or modify the Magistrate Judge's recommendations. *Id.* The Court may also receive further evidence or return the matter to the Magistrate Judge with instructions. *Id.*

When reviewing a motion to dismiss pursuant to Rule 12(b)(6), the Court must accept the complaint's factual allegations as true. *See Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555–56 (2007). Rule 8(a) requires "a short and plain statement of the claim showing that the pleader is entitled to relief." *Id.* at 555. The factual allegations do not have to be detailed, but they must provide more than labels, conclusions, or a "formulaic recitation" of the claim elements. *Id.* ("Factual allegations must be enough to raise a right to relief above the speculative level … on the assumption that all the allegations in the complaint are true (even if doubtful in fact)."). Moreover, there must be sufficient factual matter to state a facially plausible claim to relief. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). The facial plausibility standard is satisfied when the complaint's factual content "allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id.* ("Where a complaint pleads facts that are merely consistent with a defendant's liability, it stops short of the line between possibility and plausibility of entitlement to relief." (cleaned up)).

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To prevail on a claim of induced infringement, the plaintiff must show that: (1) there is an underlying act of direct infringement, (2) the alleged infringer knowingly induced the infringement, and (3) the alleged infringer possessed specific intent to encourage the acts of direct infringement. *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018). "[A] patented method of using a drug can only be infringed under § 271(e)(2) by filing an ANDA that seeks approval to market the drug for that use." *AstraZeneca Pharms. LP v. Apotex Corp.*, 669 F.3d 1370, 1379 (Fed. Cir. 2012). A generic manufacturer can be liable for inducing infringement of a patented method even when the generic has attempted to "carve out" the patented indications. *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, 7 F.4th 1320, 1338 (Fed. Cir. 2021) (per curiam).

Rule 15(a)(2) states that, apart from amendments as a matter of course, "a party may amend its pleading only with the opposing party's written consent or the court's leave. The court should freely give leave when justice so requires." FED. R. CIV. P. 15(a)(2). The Third Circuit has construed Rule 15 liberally, instructing that "absent undue or substantial prejudice, an amendment should be allowed under Rule 15(a) unless 'denial [can] be grounded in bad faith or dilatory motive, truly undue or unexplained delay, repeated failure to cure deficiency by amendments previously allowed or futility of amendment.'" *Long v. Wilson*, 393 F.3d 390, 400 (3d Cir. 2004) (quoting *Lundy v. Adamar of New Jersey, Inc.*, 34 F.3d 1173, 1196 (3d Cir. 1994)) (emphasis omitted). An amendment is futile if it "would fail to state a claim upon which relief could be granted." *In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1434 (3d Cir. 1997). The futility analysis follows the standard that applies to a motion under Rule 12(b)(6). *Id.*

II. DISCUSSION

A. Defendants' Motion to Dismiss

Zogenix, Inc. and Zogenix International Ltd. ("Plaintiffs") sell Fintepla® for the treatment of seizures associated with Dravet syndrome. (C.A. No. 22-1232-RGA, D.I. 1 at 2). The active ingredient in Fintepla® is fenfluramine hydrochloride ("fenfluramine"). (*Id.* at 7). U.S. Patent Nos. 10,478,441 (the "'441 Patent") and 10,478,442 (the "'442 Patent") are listed in the FDA's Orange Book for Fintepla®. (D.I. 102, Ex. F). The '441 and '442 Patents are directed to, *inter alia*, the use of fenfluramine in combination with stiripentol. '441 Patent; '442 Patent. In October of 2021, Apotex Inc. and Apotex Corp. ("Defendants") notified Plaintiffs that they had filed an Abbreviated New Drug Application ("ANDA") seeking FDA approval to market a generic version of Fintepla®. (D.I. 95, Ex. A at 12). Defendants submitted a section viii certification for the '441 and '442 Patents, representing that the methods of use claimed in those patents are carved out from Defendants' label. (*Id.* at 13).

U.S. Patent No. 11,406,606 (the "'606 Patent") is also listed in the Orange Book for Fintepla® and, like the '441 and '442 Patents, is directed to methods of treating patients with Dravet syndrome by administering a combination of stiripentol and reduced dosages of fenfluramine. (C.A. No. 22-1232-RGA, D.I. 1 at 11–12). On September 21, 2022, Plaintiffs asserted causes of action against Defendants for infringement of the '606 Patent under 35 U.S.C. § 271(e)(2)(A) (Count I) and declaratory judgment of infringement of the '606 Patent (Count II). (C.A. No. 22-1232-RGA, D.I. 1). The asserted claims of the '606 Patent require the use of fenfluramine in combination with stiripentol. Asserted claim 15 of the '606 Patent recites a method of reducing or controlling seizures in a patient by "reducing a dosage of fenfluramine … by 30% to 60% based on the patient being treated with a therapeutically effective amount of

stiripentol, whereby the dosage of fenfluramine … is reduced as compared to an amount of fenfluramine … without stiripentol." '606 Patent, Claim 15.

Defendants' motion to dismiss is limited to Plaintiffs' assertion of the '606 Patent. (C.A. No. 22-1232-RGA, D.I. 14 at 1). The Report recommends that I grant Defendants' motion to dismiss Plaintiffs' induced infringement claims under Rule 12(b)(6) for failure to state a claim upon which relief can be granted. (D.I. 154 at 10).

Plaintiffs object to the Magistrate Judge's conclusion that Plaintiffs' complaint does not plausibly allege that Defendants' ANDA label (C.A. No. 22-1232-RGA, D.I. 16, Ex. C (hereinafter "ANDA Label")) encourages or instructs an infringing use. (D.I. 165). Plaintiffs argue, "[T]he R&R erroneously applied its own interpretation of [Defendants'] label instead of crediting Plaintiffs' allegations, which concerned how a *prescribing physician* would read the label." (*Id.* at 2–3 (emphasis in original)). Specifically, Plaintiffs contend that the Magistrate Judge "improperly focuse[d] on individual sections of [Defendants'] label in isolation," whereas a prescribing physician would "read the label as a whole." (*Id.* at 3). When read as a whole, Plaintiffs say, the label implicitly encourages an infringing use—namely, the co-administration of fenfluramine and stiripentol. (D.I. 165 at 3).

Plaintiffs highlight three aspects of the label to support their position: (1) the warnings and side effects of fenfluramine in § 12.1; (2) the dosing instructions in §§ 2.3, 2.4, 7.1, and 8.6; and (3) the clinical study data in §§ 6.1 and 14.1. None of these, either alone or in combination, are sufficient. Plaintiffs' argument is as follows. First, Plaintiffs argue that § 12.1—which warns of an association between drugs like fenfluramine and certain cardiac side-effects—encourages lower doses of fenfluramine. (*Id.* at 3). Second, Plaintiffs argue that the dosing instructions in §§ 2.3, 2.4, 7.1, and 8.6 "instruct a physician that administering stiripentol with fenfluramine

enables lower dosages of fenfluramine, as encouraged by § 12.1...." (*Id.* at 3–4). Plaintiffs reach this conclusion by examining the interplay between these provisions. Section 2.3 instructs a 20 mg dosage of fenfluramine for patients on strong CYP inhibitors not taking concomitant stiripentol. (ANDA Label at APO-FEN-00005694). It then directs physicians to § 7.1, which prescribes a 17 mg fenfluramine dosage for patients taking strong CYP inhibitors and "another AED."[2] (*Id.* at APO-FEN-00005700). Similar dosage modification instructions appear in §§ 2.4 and 8.6. (*See id.* at APO-FEN-00005694, APO-FEN-00005702). According to Plaintiffs, "A physician reading these sections would recognize that 'another AED' could *only* be stiripentol and not some other AED like valproate," as any other interpretation would render the instructions "internally inconsistent." (D.I. 165 at 4). Consequently, Plaintiffs say, these sections encourage a physician to co-administer fenfluramine with stiripentol. (*Id.* at 3–4, 7–8).

Third, Plaintiffs argue, "[A] physician would recognize [Defendants'] label as instructing that administering fenfluramine with other AEDs, and specifically stiripentol, is safe and effective for treating seizures associated with Dravet syndrome." (D.I. 165 at 4–5). Plaintiffs mainly rely on the label's description of safety and efficacy data from two clinical studies—one (Study 1), which § 14.1 describes as treating "patients who were not receiving stiripentol," and another (Study 2), which § 14.1 describes as treating "patients who were receiving other AEDs." (ANDA Label at APO-FEN-00005706–07). These studies also appear in § 6.1, which refers to two clinical trials of fenfluramine with patients who were taking "concomitant standard of care AEDs." (*Id.* at APO-FEN-00005698). The label does not identify stiripentol as an AED used in Study 2.

[2] AED stands for anti-epileptic drug. (D.I. 172 at v).

Nevertheless, Plaintiffs say that a physician, reading these sections together, would understand that the "other AEDs" tested in Study 2 must have included stiripentol. (D.I. 165 at 5). Plaintiffs explain, "[W]hile the physician does not need to rely on outside material to understand the implications of the [Defendants'] label, they could easily find additional information that would confirm their understanding." (*Id.* at 9). For example, Plaintiffs stress that there are only several approved AEDs. (*Id.* at 5 n. 2; D.I. 156 at 22:6–23:9).

Plaintiffs also point to § 2.2, which provides dosing instructions. (ANDA Label at APO-FEN-00005693–94). Plaintiffs say that the instructions in § 2.2 "*are not* limited to patients who are not on concomitant stiripentol," and that, consequently, "physicians would recognize that these instructions apply to both patients on *and* patients not on concomitant stiripentol...." (D.I. 165 at 7 (emphasis in original)). Plaintiffs argue that this section provides "additional context" to Defendants' label that, in combination with §§ 6.1 and 14.1, instructs that co-administration of fenfluramine with stiripentol is safe and effective. (*Id.* at 4–5, 7).

Plaintiffs do not convince me. I do not think that the whole of the label is any greater than the sum of its parts. And I agree with the Magistrate Judge that its parts—that is, the portions of the label upon which Plaintiffs rely—do not encourage or instruct an infringing use.

I begin with § 12.1. I agree with the Magistrate Judge that Plaintiffs' reliance on the warning language in § 12.1 is unavailing. In brief, warnings are not instructions. *See Amarin Pharma, Inc. v. Hikma Pharmaceuticals USA Inc.*, 578 F. Supp. 3d 642, 646 (D. Del. 2022) (quoting *Otsuka Pharm. Co. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 490 (D.N.J. 2015) for the proposition that "a warning is just that—a warning. It is not an instruction."), *appeal docketed*, No. 23-1169 (Fed. Cir. Nov. 21, 2022).

As the Magistrate Judge notes (D.I. 154 at 12–13), the Federal Circuit rejected a similar inducement argument in *HZNP Medicines LLC v. Actavis Lab'ys*, 940 F.3d 680 (Fed. Cir. 2019). There, the patented method required three steps: (1) applying the topical medication, (2) waiting for the area to dry, and (3) applying "sunscreen, insect repellant, or a second topical medication." *Id.* at 702. The relevant portion of the generic's label stated, "Wait until the treated area is dry before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication to the same knee you have just treated with [the topical medication]." *Id.* at 700. The Court held that the generic's label did not "encourage infringement," as the label only required the first step of the patented method; the label permitted, but did not require, the subsequent application of sunscreen, insect repellant, or a second medication. *Id.* at 702. Consequently, the Court concluded that although the evidence "establishe[d] that some users might infringe," it did "not establish that the proposed label instructs users to perform the patented method." *Id.* (cleaned up).

Here, the warning language in § 12.1 constitutes even less of an instruction than the portion of the label at issue in *HZNP*. Indeed, § 12.1 gives no instructions at all. I agree with Defendants that § 12.1, at most, "suggests an association between drugs like fenfluramine and certain adverse effects and is therefore a warning." (D.I. 172 at 3). This section, standing alone, does not instruct physicians to administer lower doses of fenfluramine. Plaintiffs do not attempt to distinguish *HZNP* with respect to § 12.1. Instead, Plaintiffs contend that § 12.1 "provides context for the express instructions to reduce fenfluramine dosages in other sections of [Defendants'] label." (D.I. 165 at 6). I therefore turn to those sections now, keeping § 12.1 in mind.

Next, §§ 2.3, 2.4, 7.1, and 8.6. These portions of the label don't help Plaintiffs either, even when they are read in the context of § 12.1. I agree with Defendants (D.I. 172 at 6) that Plaintiffs' argument—that the phrase "another AED" means stiripentol to the exclusion of other AEDs (D.I. 165 at 4)—asks me to disregard the plain text of the label. I do not find it plausible that a physician would understand "another AED" to mean anything other than "another AED," and Plaintiffs do not dispute that multiple AEDs exist besides stiripentol. (*E.g.*, D.I. 156 at 20:18–21 (identifying clobazam and valproate as AEDs that are "also frequently used in the treatment [of] Dravet [syndrome]")). Notably, every explicit reference to stiripentol in the dosing instructions at issue describes the administration of fenfluramine "without concomitant stiripentol." (*E.g.*, ANDA Label at APO-FEN-00005694 (§§ 2.3, 2.4)). Such language hardly constitutes encouragement to prescribe fenfluramine in conjunction with stiripentol.

Plaintiffs run into the same problem with § 2.2. Plaintiffs maintain that the instructions in § 2.2 "apply to both patients on *and* patients not on concomitant stiripentol...." (D.I. 165 at 7). But as Defendants note (D.I. 172 at 7–8), the starting and maintenance dosages listed in § 2.2 refer to a recommended titration schedule for fenfluramine that is labeled, "without concomitant stiripentol." (ANDA Label at APO-FEN-00005693 (Table 1)). Again, the label here excludes, rather than encourages, the co-administration of fenfluramine and stiripentol. Indeed, the Magistrate Judge specifically cited the "without concomitant stiripentol" language in § 2.2 as an example of how "[Defendants'] label carves out references to fenfluramine administered concomitantly with stiripentol." (*See* D.I. 154 at 11, 13). I agree with the Magistrate Judge. Section 2.2 does not provide any "additional context" § 2.2 that is helpful for Plaintiffs' argument.

Finally, §§ 14.1 and 6.1. I do not agree with Plaintiffs that "the description of Study 2 confirms to physicians that it necessarily included stiripentol." (D.I. 165 at 9). Plaintiffs' position requires reading the label's references to Study 2 such that "other AEDs" mentioned in § 14.1, and "concomitant standard of care AEDs" mentioned in § 6.1, necessarily include stiripentol. As explained above with respect to §§ 7.1 and 8.6, this argument asks me to disregard the plain language of the label.

Furthermore, I agree with the Magistrate Judge that, "[e]ven if the reference to AEDs in Study 2 is read to encompass a potentially infringing use of fenfluramine in combination with stiripentol, the label's inclusion of both infringing and non-infringing uses is not sufficient to 'specifically encourage' the use of the generic for the patented indication." (D.I. 154 at 15). *Amarin* and *Grunenthal* are instructive. Both cases involved label indications that encompassed both infringing and non-infringing uses, but which provided no further instructions as to the infringing use. *Amarin*, 578 F. Supp. 3d at 647 (allegation that defendant advertised its product in a therapeutic category including infringing uses was insufficient to plead inducement "without a label or other public statements instructing as to infringing use."); *Grunenthal GmbH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) ("[E]ven if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain. Therefore, the proposed ANDA labels do not specifically encourage use of tapentadol hydrochloride for treatment of polyneuropathic pain."). Here, counter to Plaintiffs' contentions (D.I. 165 at 10), I do not think that the label's dosing instructions and clinical study descriptions provide any more instruction to infringe than there was in *Amarin* and *Grunenthal*.

I therefore grant Defendants' motion to dismiss Plaintiffs' induced infringement claims under Rule 12(b)(6) for failure to state a claim upon which relief can be granted.

B. Defendants' Motion to Amend

An initial dispute concerns the standard of review to be applied. For non-dispositive motions, such as a motion for leave to amend, the Court reviews findings of fact for clear error and conclusions of law *de novo*. *Cornell Univ. v. Illumina, Inc.*, 2017 WL 89165, at *8 (D. Del. Jan. 10, 2017). The Magistrate Judge denied Plaintiffs' request to amend (with respect to the '606 Patent) and motion to amend (with respect to the '510, '441, and '442 Patents) on the basis of futility, relying on the same reasoning as she applied for granting the motion to dismiss. (*See* D.I. 154 at 19, 22). Plaintiffs argue, "Because the futility analysis is based on whether or not an amended complaint could survive a motion to dismiss," review of the motion to amend should also be *de novo*. (D.I. 165 at 2). Defendants disagree. (D.I. 172 at 2 n. 1).

I agree with Plaintiffs. "The standard for assessing futility is the 'same standard for legal sufficiency as applies under [Federal] Rule [of Civil Procedure] Rule 12(b)(6).'" *Great W. Mining & Min. Co. v. Fox Rothschild, LLP*, 615 F.3d 159, 175 (3d Cir. 2010) (quoting *Shane v. Fauver*, 213 F.3d 113, 115 (3d Cir. 2000)). That determination—whether a claim survives a 12(b)(6) motion—is a "purely legal question." *Barefoot Architect, Inc. v. Bunge*, 632 F.3d 822, 835 (3d Cir. 2011). Therefore, I will review the Magistrate Judge's determinations here *de novo*.

1. The '606 Patent

Plaintiffs request leave to amend their Complaint pursuant to Rule 15(a)(2) if the Court finds dismissal appropriate. (C.A. No. 22-1232-RGA, D.I. 27 at 20). Plaintiffs note that they filed their Complaint before Defendants' most recent amendment to the ANDA label. (*Id.*). That version of the label (C.A. No. 22-1232-RGA, D.I. 16, Ex. C) is the one discussed in the Report and analyzed above.

"The standard for assessing futility is the same standard for legal sufficiency as applies under Federal Rule of Civil Procedure Rule 12(b)(6)." *Great W. Mining & Min. Co.*, 615 F.3d at 175 (cleaned up). The Magistrate Judge decided that Plaintiffs have not adequately alleged that Defendants' label induces infringement of the asserted method claim of the '606 Patent. (D.I. 154 at 18). The Magistrate Judge therefore concluded that Plaintiffs "have failed to establish how an amended pleading would not be futile," and denied Plaintiffs' request. (*Id.* at 19).

As explained, I agree with the Magistrate Judge with respect to the adequacy of Plaintiffs' inducement allegations. *See supra* Section II.A. I therefore conclude the same with respect to Plaintiffs' request to amend their Complaint. Thus, I deny Plaintiffs' request.

2. The '510, '441, and '442 Patents

Plaintiffs move to amend their complaint to assert infringement of three additional patents—the '441 Patent, the '442 Patent, and U.S. Patent No. 10,351,510 (the "'510 Patent")—and join additional plaintiffs. (D.I. 95). The Report granted-in-part Plaintiffs' motion to amend under Rule 15(a). (D.I. 154 at 2). Specifically, the Report granted the motion with respect to claims pertaining to the '510 Patent and denied the motion with respect to claims pertaining to the '441 and '442 Patents. (*Id.* at 22–23).

The latter decision is, once again, because of futility. The asserted claims of the '441 and '442 Patents require the use of fenfluramine in combination with stiripentol. (D.I. 95, Ex. A, Ex. 3–4). Consequently, for the reasons discussed with respect to the '606 Patent, the Magistrate Judge concluded that the amended pleading does not plausibly state a claim for induced infringement of the '441 and '442 Patents based on Defendants' ANDA label. (D.I. 154 at 22).

For those same reasons, I agree with the Magistrate Judge. I therefore deny Defendants' motion to amend their Complaint with respect to the '441 and '442 Patents.

III. CONCLUSION

For the reasons discussed above, I will adopt the Magistrate Judge's Report & Recommendation. An appropriate order will issue.

Signed this 8th day of September, 2023.

United States District Judge

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ORDER

For the reasons stated in the accompanying Memorandum,

- The Report & Recommendation (D.I. 154) is ADOPTED.
- Defendants' motion to dismiss Plaintiffs' induced infringement claims with respect to the '606 Patent (No. 22-1232-RGA, D.I. 14) is GRANTED. These claims are DISMISSED for failure to state a claim.
- Plaintiffs' request for leave to amend their complaint with respect to the '606 Patent (No. 22-1232-RGA, D.I. 27 at 20) is DENIED.
- Plaintiffs' motion for leave to amend their complaint with respect to the '441 and '442 Patents (D.I. 95) is DENIED.

IT IS SO ORDERED.

Entered this 8th day of September, 2023.

United States District Judge