United States Court of Appeals for the Federal Circuit

JAZZ PHARMACEUTICALS, INC.,
Plaintiff-Appellee

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant

2024-2274

Appeal from the United States District Court for the District of Delaware in No. 1:21-cv-00691-GBW, Judge Gregory Brian Williams.

JAZZ PHARMACEUTICALS, INC., JAZZ PHARMACEUTICALS IRELAND LIMITED,
Plaintiffs-Appellees

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant

2024-2277

Appeal from the United States District Court for the District of Delaware in No. 1:21-cv-01138-GBW, Judge Gregory Brian Williams.

JAZZ PHARMACEUTICALS, INC., JAZZ PHARMACEUTICALS IRELAND LIMITED,
Plaintiffs-Appellees

v.

AVADEL CNS PHARMACEUTICALS, LLC,
Defendant-Appellant

2024-2278

Appeal from the United States District Court for the District of Delaware in No. 1:21-cv-01594-GBW, Judge Gregory Brian Williams.

Decided: May 6, 2025

FRANK CALVOSA, I, Quinn Emanuel Urquhart & Sullivan, LLP, New York, NY, argued for plaintiff-appellee. Also represented by GABRIEL P. BRIER, FRANCIS DOMINIC CERRITO, QUENTIN JORGENSEN, ELLYDE R. THOMPSON; ISAAC SAIDEL-GOLEY, Boston, MA.

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NY; KIRA ALEXIS DAVIS, Morrison & Foerster LLP, Los Angeles, CA; DARALYN JEANNINE DURIE, San Francisco, CA; DANIEL M. SILVER, McCarter & English, LLP, Wilmington, DE.

Before LOURIE, REYNA, and TARANTO, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Avadel CNS Pharmaceuticals, LLC ("Avadel") appeals from the decision of the U.S. District Court for the District of Delaware permanently enjoining it from seeking approval from the U.S. Food and Drug Administration ("the FDA") of its product, Lumryz, for the treatment of idiopathic hypersomnia, as well as from marketing Lumryz for that indication. *Jazz Pharms., Inc. v. Avadel CNS Pharms. LLC*, No. 21-cv-691, 2024 WL 4005200 (D. Del. Aug. 27, 2024) ("*Permanent Injunction Order*"); *see Jazz Pharms., Inc. v. Avadel CNS Pharms. LLC*, No. 21-cv-691, 2024 WL 4100159 (D. Del. Aug. 27, 2024) ("*Decision*"). As the district court later clarified in an order denying Avadel's motion to stay the injunction pending appeal, Avadel is specifically enjoined from: (1) offering open-label extensions to clinical trial participants, (2) applying for FDA approval of Lumryz for idiopathic hypersomnia, and (3) initiating new clinical trials or studies after the *Permanent Injunction Order*'s effective date. *Jazz Pharms., Inc. v. Avadel CNS Pharms. LLC*, No. 21-cv-691 (D. Del. Sep. 24, 2024) ("*Stay Order*"), J.A. 38–44.

For the following reasons, we reverse-in-part, vacate-in-part, and remand.

BACKGROUND

I

Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (collectively, "Jazz") manufacture and sell two sodium oxybate products: Xyrem®, a sodium oxybate

oral solution approved for the treatment of excessive daytime sleepiness ("EDS") and cataplexy in adult and pediatric patients with narcolepsy, and Xywav®, a low-sodium oxybate product approved for the same indications as Xyrem, as well as for the treatment of idiopathic hypersomnia. Idiopathic hypersomnia, or "IH," is a chronic neurological condition "on a spectrum with narcolepsy" that is similarly characterized by EDS. J.A. 5666. Xywav is the first and, currently, only FDA-approved treatment for IH.

Jazz is not without competition, however. On December 15, 2020, Avadel submitted a New Drug Application ("NDA") to the FDA pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2), seeking approval of its own product, Lumryz, a once-nightly formulation of sodium oxybate for the treatment of EDS and cataplexy in adults with narcolepsy. An NDA filed under that section is commonly referred to as a "paper NDA," which, unlike an Abbreviated New Drug Application ("ANDA"), requires the applicant to submit safety and efficacy data. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045–46 (Fed. Cir. 2010). But such data need not have been developed by the applicant; rather, the applicant may rely on existing FDA findings of safety and efficacy for already-approved drugs, or on other studies not performed by the applicant. *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 629 (Fed. Cir. 2015). Avadel's paper NDA relied in part on the FDA's findings of safety and efficacy for Jazz's Xyrem. J.A. 9255–56.

On March 23, 2021, three months after Avadel submitted its paper NDA, Jazz filed a patent application entitled "GHB [(*i.e.*, oxybate)] Formulation and Method for its Manufacture," which issued on October 19, 2021, as U.S. Patent 11,147,782 ("the '782 patent"). Relevant here, claims 14 and 24 of the '782 patent recite:

> 14. A unit dose comprising a formulation of gamma-hydroxybutyrate,
>
> wherein the formulation comprises:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.
>
> 24. The unit dose of claim 14, wherein the unit dose is a sachet.

'782 patent, col. 26 ll. 9–20, 54–55. The '782 patent will expire on February 18, 2036.

Neither of Jazz's Xyrem and Xywav products practices claim 24 of the '782 patent, the only asserted claim in this litigation. Indeed, the '782 patent is not listed in the Orange Book for either Xyrem or Xywav, indicating Jazz's view that the '782 patent does not claim those drugs or their use. *See* 21 U.S.C. § 355(b)(1)(A)(viii) (providing the statutory requirements for listing a patent in the Orange Book). As such, in pursuing its paper NDA for Lumryz, Avadel did not need to make—and, indeed, did not make—any patent certifications under § 355(b)(2)(A) as to the '782 patent.[1]

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[1] As with an ANDA, a paper NDA requires the applicant to submit a certification that, for example, any patent

II

On November 10, 2021, roughly one month after the '782 patent issued and eleven months after Avadel submitted its paper NDA, Jazz filed a complaint in the U.S. District Court for the District of Delaware, alleging that Avadel's FDA submission "constitute[d] infringement [of the '782 patent] under 35 U.S.C. § 271(e)(2)(A)." J.A. 10167. That statute provides:

> It shall be an act of infringement to submit an application . . . described in section 505(b)(2) of [the FDCA] for a drug claimed in a patent . . . if the purpose of such submission is to obtain approval under [the FDCA] to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent.

§ 271(e)(2)(A). In its claim for relief, Jazz sought, *inter alia*, a permanent injunction under 35 U.S.C. § 271(e)(4)(B),[2] as well as damages for any of Avadel's infringement "other than those acts expressly exempted by 35 U.S.C. § 271(e)(1)."[3] J.A. 10169–70. Accordingly, at the time of

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that "claims the drug" for which the relied-upon investigations were conducted "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." *See* § 355(b)(2)(A)(i)–(iv).

[2] For an act of infringement under § 271(e)(2), as Jazz's complaint alleged, the statute provides that "injunctive relief may be granted . . . to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug . . . ." § 271(e)(4)(B).

[3] The statute expressly excludes from infringement any infringing activities done "solely for uses reasonably related to the development and submission of information"

the initial filing of Jazz's complaint, this lawsuit appeared to fall within the bounds of the Hatch-Waxman Act insofar as the alleged infringement "ar[ose] from Avadel's *filing* of a New Drug Application." J.A. 10157 (emphasis added). That is, Jazz's claims were based on an artificial act of infringement under § 271(e)(2), and not on any actual acts of infringement under § 271(a)–(c). *See* J.A. 10167; J.A. 7741 (Avadel letter to district court explaining that "Jazz initiated this series of actions under the Hatch-Waxman Act"); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990) (explaining that § 271(e)(2) "define[s] a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications").

That changed, however, on May 1, 2023, when the FDA approved Avadel's paper NDA and on June 5, 2023, when Avadel commercially launched Lumryz.[4] Consequently, on June 8, 2023, the parties stipulated, subject to the district court's approval, to allow Jazz leave to amend its complaint. Stipulation to Amend Complaint, *Jazz Pharms., Inc. v. Avadel CNS Pharms. LLC*, No. 21-cv-1594 (D. Del. June 8, 2023), ECF No. 209. Specifically, Jazz amended its complaint to remove any allegations of "artificial"

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to the FDA. § 271(e)(1) ("the safe-harbor provision" or "the safe harbor").

[4] Because the '782 patent is not listed in the Orange Book for Xyrem, the filing of Jazz's complaint did not trigger a 30-month regulatory stay on the FDA's approval of Avadel's paper NDA. *See* 21 U.S.C. § 355(c)(3)(C); *see also* Oral Arg. 9:30–9:38, *available at* https://oralarguments.cafc.uscourts.gov/default.aspx?fl=24-2274_02072025.mp3 (counsel for Avadel noting that "the reason we're not dealing with an automatic stay is we're not dealing with an Orange Book-listed patent here. Jazz doesn't practice the patent that [it's] asserting.").

infringement under § 271(e)(2), replacing them with affirmative allegations that Avadel had and would infringe the '782 patent under each of § 271(a)–(c) by making and selling the now-FDA-approved Lumryz. *Compare* J.A. 10167–68, *with* J.A. 10007. Jazz further amended its complaint to remove its prayer for a permanent injunction under § 271(e)(4)(B), but otherwise maintained its requests for injunctive relief and damages against infringing activities, other than damages for acts exempted by § 271(e)(1). *Compare* J.A. 10169–70, *with* J.A. 10008.

Following discovery and prior to trial, the parties stipulated that Lumryz would infringe claim 24 of the '782 patent if that claim was not found to be invalid. J.A. 4312. And after a five-day trial, a jury found that Avadel had failed to prove the invalidity of that claim. J.A. 4387–89. The jury awarded Jazz a reasonable royalty of $233,562.83 for Avadel's past infringement. J.A. 4390.

III

On April 12, 2024, following trial, Jazz moved for a permanent injunction under 35 U.S.C. § 283 seeking to prevent Avadel from making, using, or selling Lumryz until expiration of the '782 patent, February 18, 2036. J.A. 4545–47. Jazz proposed to exclude from the injunction, however, Avadel's making, using, and selling Lumryz "(a) for the patients who have been prescribed Lumryz as of the effective date of the injunction . . . ; (b) in currently-ongoing clinical trials and studies; (c) to update data in old studies if necessary; and (d) to re-run necessary tests for quality control for regulators or customers." J.A. 4550. And, "[f]or the avoidance of doubt," Jazz proposed that although Avadel "may continue to use Lumryz in currently-ongoing clinical trials and studies . . . , [it] may not seek approval from the [FDA] for any indication that was not already part of Lumryz's approved product labeling as of March 4, 2024." *Id.* Jazz's motion was fully briefed, and an oral hearing was held on June 4, 2024.

While Jazz's motion was pending, on August 1, 2024, Avadel launched its REVITALYZ clinical trial, a "double-blind, placebo-controlled, randomized withdrawal, multi-center study of the efficacy and safety of Lumryz with an open-label extension period in patients diagnosed with [IH]." J.A. 7529 (citing *Safety and Efficacy of [Lumryz] in Idiopathic Hypersomnia (REVITALYZ)*, ClinicalTrials.gov, https://clinicaltrials.gov/study/NCT06525077?term=NCT06525077&rank=1). Relevant here, an open-label extension ("OLE") period "allows clinical trial participants to receive a trial drug past the formal completion of the trial, both to gather additional safety data for submission to the FDA and to maintain continuity of patient treatment." J.A. 7511–12.

On August 27, 2024, the district court granted in part Jazz's motion. Specifically, it granted a "limited permanent injunction prohibiting Avadel from seeking approval from the [FDA] and marketing Lumryz for the treatment of IH." *Permanent Injunction Order*, at *1. But, as Jazz had proposed, it excluded from the injunction Avadel's making, using, and selling Lumryz for use "in currently-ongoing clinical trials and studies." *Id.* It further adopted Jazz's proposed language that, "[f]or the avoidance of doubt, . . . while Avadel may continue to use Lumryz in currently-ongoing clinical trials and studies . . ., Avadel may not seek approval of Lumryz from the FDA for the treatment of IH or for any indication that was not already part of Lumryz's approved product labeling as of March 4, 2024." *Id.* Avadel filed a Notice of Appeal the next day. J.A. 341.[5]

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[5] The district court also denied in part Jazz's motion. Specifically, the court refused to enjoin Avadel from making, using, and selling Lumryz for the treatment of narcolepsy—its FDA-approved indication. *See Decision*, at *1. The court found that enjoining such activities threatened a

IV

One week later, on September 3, 2024, Avadel filed an emergency motion in the district court to stay the injunction pending appeal, arguing that enjoining Avadel from initiating new clinical trials and seeking approval from the FDA to market Lumryz for the treatment of IH (or any other indication) "overlook[ed] a crucial feature of federal patent law"—the safe-harbor provision. J.A. 7496. Avadel argued that, under the safe harbor, the enjoined activities are "entirely non-infringing," such that the injunction exceeds its lawful scope. J.A. 7502. And it told the court that Jazz had demanded that, pursuant to the injunction, Avadel cease enrolling new patients in its ongoing REVITALYZ trial and "terminate the [OLE] period for those who ha[d] already been enrolled" and prescribed Lumryz as part of that trial. J.A. 7511. Jazz opposed the motion, arguing that Avadel's arguments were misplaced because the safe harbor is an affirmative defense that Avadel never pleaded or pursued, and that therefore had been waived. J.A. 7542.

In a memorandum order, the district court denied Avadel's motion to stay the injunction. *See Stay Order*, J.A. 39. In doing so, the court "[found] it pertinent to discuss and clarify the scope of conduct enjoined." *Id.*, J.A. 40. It began by clarifying what activities were *not* covered by the injunction. Under the injunction's "explicit terms," the district court explained, Avadel may continue to make, use, and sell Lumryz for its REVITALYZ clinical study because that trial was initiated prior to entry of the injunction. *Id.*,

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"substantial harm to the public interest" that outweighed any irreparable injury to Jazz. *Id.* at *9. Instead, the court determined that Jazz is entitled to a reasonable royalty for Avadel's ongoing sales of Lumryz for narcolepsy. *Id.* at *13. Jazz does not appeal from that partial denial, so we do not address it further.

J.A. 40–41. It further clarified that Avadel was not enjoined from enrolling new subjects in that already ongoing study. *Id.* at 41. And finally, it stated that, "while the [*Permanent Injunction Order*] enjoins Avadel from seeking FDA approval for IH, [it] does not enjoin Avadel from *submitting information or results* from ongoing studies to the FDA." *Id.*

The district court then clarified that Avadel *is* enjoined from: "(1) offering open-label extensions to [REVITALYZ] trial participants; (2) applying for FDA approval of Lumryz for IH; and (3) initiating *new* clinical trials or studies after the [*Permanent Injunction Order*]'s effective date." *Id.* Having clarified the specific activities precluded by the injunction, the court proceeded to determine whether Avadel had made the requisite showings as to each of those activities to warrant a stay. And finding that Avadel had not demonstrated a substantial risk of immediate and irreparable harm for any of those activities, the district court denied the motion. *Id.*

Avadel timely amended its Notice of Appeal to include both the *Permanent Injunction Order* and the *Stay Order*. *Jazz Pharms.*, No. 21-cv-1594 (D. Del. Sep. 27, 2024), ECF No. 584. We have jurisdiction under 28 U.S.C. § 1292(c)(1).[6]

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[6] On October 2, 2024, a motions panel of this court granted Avadel's motion to stay the district court's injunction "insofar as it enjoins 'initiating new clinical trials or studies,'" but declined to stay the injunction in all other respects due to Avadel's "failure to establish irreparable injury." Appeal No. 24-2274, ECF No. 30.

DISCUSSION

I

An injunction is a "drastic and extraordinary remedy" rooted in well-established principles of equity. *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1359 (Fed. Cir. 2013) (quoting *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 165 (2010)). To show entitlement to a permanent injunction, a plaintiff must establish: "(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction" ("the *eBay* factors"). *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). "[D]istrict courts are frequently admonished not to issue sweeping injunctions against potentially infringing activities in patent cases, but to restrict the scope of the injunction to the particular adjudicated infringing activity." *Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1344 (Fed. Cir. 2012) (collecting cases). Permanent injunctions of proper scope are provided for by law. But this is not such a case.

We review the district court's grant of a permanent injunction and the scope of that injunction for abuse of discretion. *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 772 (Fed. Cir. 1993). "An abuse of discretion may be established by showing that the court made a clear error of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings." *Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1367 (Fed. Cir. 1996). Legal error therefore constitutes an abuse of discretion. *See id.*

II

For clarity and precision, we address each of the individually enjoined activities separately. Those activities are (1) initiating new clinical trials for Lumryz, (2) offering open-label extensions in ongoing clinical trials, and (3) applying for FDA approval of Lumryz for IH. *See Stay Order*, J.A. 41.

A. Initiating New Clinical Trials for Lumryz

In 1984, Congress enacted the Hatch-Waxman Act with one of its purposes being "mak[ing] available more low cost generic drugs." H.R. Rep. No. 98-857, pt. 1, at 14 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. To that end, Congress created the safe-harbor provision, § 271(e)(1), "to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement." *Id.* at 45–46 (abrogating *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984)). Congress determined that "experimental activity does not have any adverse economic impact on the patent owner's exclusivity during the life of a patent, but prevention of such activity would extend the patent owner's commercial exclusivity beyond the patent expiration date." *Id.* at 46 (also emphasizing that, upon patent expiration, "immediate competition should be encouraged"). As such, Congress provided that, "[i]n any action for patent infringement brought under [§ 271], *no injunctive or other relief may be granted* which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under [the safe-harbor provision, § 271(e)(1)]." 35 U.S.C. § 271(e)(3) (emphasis added).

The plain language and purposes of the Hatch-Waxman Act make it clear that enjoining Avadel from initiating new clinical trials for Lumryz (for IH or otherwise) until expiration of the '782 patent is unlawful and, therefore, an

abuse of discretion. That activity is statutorily non-infringing under § 271(e)(1) and statutorily precluded from being enjoined under § 271(e)(3). As the Supreme Court has explained, it is "apparent from the statutory text" that § 271(e)(1) "exempt[s] from infringement . . . all uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA . . . necessarily includ[ing] preclinical studies of patented compounds that are appropriate for submission to the FDA." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). The injunction prohibiting Avadel from initiating new clinical trials is therefore overbroad as a matter of law.

Resisting that conclusion, Jazz challenges that the safe harbor provides an "affirmative defense" requiring factual development that Avadel failed to plead or develop in the district court such that it is waived. Jazz Br. 29–42. Jazz argues, for example, that "Avadel presented no evidence that each use of Lumryz in each future clinical trial" qualifies for safe-harbor protection, and that "Avadel has not proved . . . that its IH activities are *solely* for uses reasonably related to the development and submission of information to the FDA." *Id.* at 45–47. We are unpersuaded.

Jazz is correct that, in some circumstances, reliance on the safe harbor requires factual development. *E.g.*, *Amgen Inc. v. Hospira, Inc.*, 944 F.3d 1327, 1337 (Fed. Cir. 2019); *Edwards Lifesciences Corp. v. Meril Life Scis. Pvt. Ltd.*, 96 F.4th 1347, 1353 (Fed. Cir. 2024). But that is because applicability of the safe harbor typically arises in situations where the patent owner alleges that certain past or current activities of the defendant, activities that the defendant believes fall within the scope of the safe harbor, constitute infringement. In those cases, then, there is a burden on the defendant to establish *in fact* that the accused activities are non-infringing under the safe harbor. And those cases are resolved when the factfinder adjudicates that issue.

This case, however, is factually and procedurally unique in our safe-harbor jurisprudence. The subject of this appeal is not whether any current or former activities of Avadel with respect to Lumryz are infringing. Indeed, Avadel stipulated that its manufacture, use, and sale of Lumryz infringe the '782 patent. Avadel therefore does not invoke § 271(e)(1) as a defense to negate its own liability. Instead, Avadel's argument is that the district court's forward-looking injunction is unlawful on its face insofar as it necessarily enjoins Avadel from making, using, and selling Lumryz "solely for uses reasonably related to the development and submission of information" to the FDA, *i.e.*, non-infringing activities, in violation of § 271(e)(3). That *facial* challenge, contrary to Jazz's position, is a purely legal invocation of the safe harbor and does not require factual development.

We therefore reject Jazz's argument that Avadel waived its reliance on the safe-harbor provision. At most, Avadel forfeited its argument by unclearly developing it in the district court. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006) (explaining that a party forfeits undeveloped arguments on appeal). But we have discretion to consider forfeited arguments, *see In re Google Tech. Holdings LLC*, 980 F.3d 858, 863 (Fed. Cir. 2020), and we exercise that discretion here where Avadel's argument turns entirely on a legal question.

What is more, Jazz has never alleged that any of Avadel's activities with respect to its future clinical trials are infringing. Therefore, there has never been an opportunity for Avadel to develop any facts to support a safe-harbor defense as to those activities, let alone sufficient facts to allow a factfinder to adjudicate that issue. Put simply, Jazz's argument that Avadel "presented no evidence that *each use* of Lumryz in *each future clinical trial*" qualifies for safe-harbor protection is premature. Jazz Br. 46 (emphases added). As we have explained, § 271(e)(3) "makes clear that *no* injunction may issue until the § 271(e)(1)

exception has been adjudicated and ruled out." *Eli Lilly & Co. v. Medtronic, Inc.*, 915 F.2d 670, 674 (Fed. Cir. 1990), *superseded by statute on other grounds as discussed in Rotec Indus., Inc. v. Mitsubishi Corp.*, 215 F.3d 1246, 1251 (Fed. Cir. 2000). Thus, Jazz's additional argument that, even if initiating new clinical trials is non-infringing, the district court has discretion to "narrowly enjoin[]" non-infringing activities "as necessary to prevent infringing conduct," falls short. *See* Jazz Br. 57–60 (citing *TiVo Inc. v. EchoStar Corp.*, 646 F.3d 869, 890 n.9 (Fed. Cir. 2011) (en banc)). Although that may be true in other contexts, Jazz's argument cannot be squared with the plain language of § 271(e)(3), which leaves no room for such discretion here.

Accordingly, we reverse the district court's injunction prohibiting Avadel from initiating any new clinical trials for Lumryz as unlawfully overbroad. Reversal, as opposed to vacatur, is appropriate here where the enjoined activities have never been accused of infringement. As such, there is no support in the record to sustain a determination one way or the other on whether the safe-harbor provision applies to those activities. *Cf. Eli Lilly*, 915 F.2d at 674–75 (vacating permanent injunction that preemptively carved out § 271(e)(1) activities where merits case had been remanded for trial on the applicability of the safe harbor to those accused activities).

We do note that our conclusion does not necessarily leave Jazz without recourse. If Jazz comes to believe that Avadel is making, using, or selling Lumryz, a product adjudicated to be infringing, for uses other than those "reasonably related to the development and submission of information" to the FDA, Jazz is free to challenge those activities.[7] At that point, we agree that, to negate liability, it

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[7] We do not speculate which activities may, in light of the district court's refusal to enjoin Avadel from making,

may be "incumbent upon Avadel to plead" its entitlement to safe-harbor protection as to each of those accused activities. Jazz Br. 32. But to enjoin Avadel outright from those activities at this juncture, before they have been adjudicated to infringe, exceeds the bounds of the law.

B. Offering OLEs in Ongoing Clinical Trials

Next, we consider the scope of the injunction insofar as it enjoins Avadel from offering OLEs to trial participants, including those currently enrolled in the ongoing REVITALYZ trial. *See Stay Order*, J.A. 41. As noted above, OLEs allow clinical trial participants to continue taking the drug after their trial participation is complete. *See* J.A. 7512. This may be done to maintain continuity of patient treatment and to "better characterize the safety of a drug late in its development." *Id.* (citing *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers*, U.S. Dep't of Health & Hum. Servs. (2017), https://www.fda.gov/media/85675/download). Pursuant to the district court's clarification of the injunction, *see Stay Order*, J.A. 41, Avadel cannot offer this OLE period to patients enrolled in the ongoing REVITALYZ trial. As such, those patients will be terminated from Lumryz treatment upon the end of their participation in the trial.

The parties debate extensively on appeal the nature of OLEs and whether Avadel's use of OLEs is an activity protected by the safe harbor. We do not comment on those arguments. Those arguments were not raised in the district court until Avadel's emergency motion to stay the injunction pending appeal. Therefore, the district court only addressed that activity in the context of clarifying the scope of the injunction—not whether those activities could or should be enjoined in the first place pursuant to the *eBay*

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using, or selling Lumryz for narcolepsy, be suitable for such a claim.

factors. Moreover, much like Avadel's activities related to its future clinical trials discussed above, whether Avadel's use of an OLE period is a safe-harbor activity is a question of fact that has not yet been accused, let alone adjudicated.

Accordingly, because this activity has never been accused of infringement, and because "[t]he statute clearly requires that the § 271(e)(1) issue be decided prior to the grant of injunctive relief," *Eli Lilly*, 915 F.2d at 674, we reverse the injunction insofar as it enjoins Avadel from offering OLEs to patients in clinical trials. Only if and when that activity is adjudicated to fall outside the protection of the safe harbor, and only if and when the district court finds the *eBay* factors to favor an injunction, may it be permanently enjoined.

C. Applying for FDA Approval of Lumryz for IH

Finally, we consider whether the district court abused its discretion by enjoining Avadel from applying for FDA approval of Lumryz for any indication that was not part of its label as of March 4, 2024. For the following reasons, we vacate the injunction in this respect and remand.

Avadel argues that enjoining it from submitting an application for FDA approval of the IH indication constituted legal error because the Hatch-Waxman Act "makes clear that seeking FDA approval in and of itself is not infringing activity." Avadel Br. 24. Avadel's argument is two-pronged. First, it argues that "the mere submission of an FDA application" is not a "use" of a patented invention and therefore not an infringement under § 271(a). *Id.* Alternatively, it argues that, even if the submission is a "use," the safe harbor provides that "uses reasonably related to the . . . submission of information" to the FDA are non-infringing. *Id.* at 24–25. And because "[a]n application for FDA approval *is* a 'submission of information' to the FDA," that application is necessarily non-infringing. *Id.* at 25.

We agree that the submission of an application to the FDA is not infringement under § 271(a). That activity is not a making, using, offering to sell, selling, or importing of a patented invention. And because applicability of the safe harbor is dependent on there being a predicate infringing activity (indeed, absent an infringing act, there would be no need for safe-harbor protection), submitting an application for FDA approval is not an activity that triggers the safe harbor.

Although we need not reach Avadel's alternative argument that submitting an application to the FDA, even if it were an infringing "use," would be protected under the safe harbor, we briefly note that the argument rests on a misreading of the statute. The "solely for uses" clause of § 271(e)(1) *modifies* the infringing act—it does not define the infringing act itself. That is, the inquiry looks to the alleged infringing activity—the making, using, selling, offering to sell, or importing—and asks whether the purpose of *that* activity was "solely for uses reasonably related to the . . . submission of information" to the FDA. § 271(e)(1); *see Amgen*, 944 F.3d at 1339. It does not follow from the plain language that the "submission of information" itself is non-infringing under that provision.

But concluding that the submission of an application to the FDA is not infringement under § 271(a) does not end the matter because that activity *is* infringement under § 271(e)(2). That section, which neither party meaningfully addresses on appeal, provides:

> It *shall be an act of infringement to submit an application* under section 505(j) of the [FDCA] or described in section 505(b)(2) of [the FDCA] for a drug claimed in a patent or the use of which is claimed in a patent.

§ 271(e)(2)(A) (emphasis added). That language plainly states that the *submission* of an ANDA (under section 505(j) of the FDCA) or a paper NDA (under section

505(b)(2) of the FDCA) for a drug claimed in a patent is an act of infringement. That understanding is consistent with precedent (and our conclusion above) that such submissions are not *actual* acts of infringement under § 271(a) because they are not a making, using, or selling of the patented invention, but instead *artificial* acts of infringement that provide a basis for litigation. *See Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("The act of infringement that gives rise to a case or controversy under section 271(e)(2) has been stated to be 'artificial,' in the sense that a specific infringing composition has not yet been made, used, or sold, and is thus not necessarily available for a court to compare to the claims." (quoting *Eli Lilly*, 496 U.S. at 677)). Even Avadel admits that the submission of an ANDA under section 505(j) of the FDCA would be "an act of artificial infringement if the purpose of the submission is to obtain approval with respect to 'a drug claimed in a patent or the use of which is claimed in a patent.'" Avadel Br. 24 n.7 (quoting § 271(e)(2)(A)). Curiously, however, Avadel leaves out of its recitation of the statutory language that the submission of a paper NDA under section 505(b)(2) of the FDCA is also an artificial act of infringement when it is done for that purpose. And that is where we observe a critical, unresolved, and unbriefed issue underlying the parties' arguments on appeal.

As noted above, Avadel's initial submission for approval of Lumryz for the treatment of narcolepsy was a paper NDA filed under § 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2). *See* J.A. 9255, 9267. But because Jazz's '782 patent is not listed in the Orange Book, Avadel did not submit with its application a patent certification under § 355(b)(2)(A)(iv) (a "paragraph iv" certification) as to that patent, which would have given notice to Jazz of Avadel's FDA filing and entitled Jazz to a 30-month stay of the FDA's approval of that application upon the initiation of a lawsuit. *See* § 355(c)(3)(C). One way or another, even without that paragraph iv notice, Jazz learned of Avadel's filing

and brought its claim for infringement under 35 U.S.C. § 271(e)(2)(A), alleging that Avadel's submission of its paper NDA constituted infringement.

At oral argument, Avadel argued for the first time that its paper NDA for Lumryz would not trigger a claim for infringement under § 271(e)(2) because the '782 patent is not an Orange Book patent. *See* Oral Arg. 12:06–12:13 (counsel for Avadel arguing that Avadel's supplemental NDA would not trigger § 271(e)(2) because "there's no Orange Book-listed patent, there's no paragraph iv certification that would trigger [§ 271(e)(2)] infringement"). Thus, in Avadel's view, it is not the *submission* of the paper NDA itself that triggers infringement, but the accompanying *certification* giving notice to a patent owner of that submission.[8] Put otherwise, Avadel argues that only applications for FDA approval that require paragraph iv certifications against Orange Book patents trigger infringement under § 271(e)(2). Avadel admitted at argument that that interpretation of § 271(e)(2) is "not in the text necessarily," but suggested that "the Supreme Court has read it to be." *See* Oral Arg. 11:57–12:05 (not citing authority). Jazz does not appear to have taken a firm position on this issue.

Avadel is incorrect in its assertion that it is the certification relating to an Orange Book patent that constitutes

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[8] We observe that this position may be consistent with Avadel's answer to Jazz's original complaint, which included an "Improper Hatch-Waxman Suit" defense, alleging that, based on Avadel's paper NDA for the narcolepsy indication, "Jazz is not entitled to any relief under that Statute, including a permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B)." J.A. 10381. But because this dispute transformed into one arising under § 271(a)–(c) mid-litigation, upon the FDA's approval of Lumryz, the merits of that defense were never adjudicated.

the artificial act of infringement. Section 271(e)(2) makes plain that it is the *submission* of the application, ANDA or paper NDA, that is the infringement. Further, the statute provides that such submission is infringement if it seeks approval of "a drug claimed in *a* patent or the use of which is claimed in *a* patent." § 271(e)(2) (emphases added). The provision does not mention or otherwise appear to limit the act of infringement to only Orange Book patents. Rather, its plain language would seem to render any ANDA or paper NDA submitted in the face of any existing patent that claims the applied-for drug or its use to be an act of infringement.

On the other hand, the placement of § 271(e)(2) within the context of the Hatch-Waxman Act suggests that the provision may only apply where the ANDA or paper NDA seeks approval of a drug claimed in an Orange Book patent. That interpretation would comport with Congress's intention of triggering litigation, after notice is given to a patent owner and regulatory approval is stayed, to hasten the introduction of generic drugs to the market if the relevant patents are found to be invalid or not infringed. Indeed, portions of the legislative history of the Act suggest that Congress "expect[ed] that infringement actions . . . w[ould] only be brought in the instance described in section 271(e)(2), where a party submitting an [ANDA] *certifies* that a patent is invalid or non-infringed and *gives the required notice of that certification* to the patent owner." H.R. Rep. No. 98-857, pt. 1, at 46 (emphases added). After all, we have not been made aware of any cases before or after the enactment of the Hatch-Waxman Act where a regulatory filing alone was held to be a patent infringement.

Nonetheless, as the issue was raised only at oral argument and not briefed, we leave it for the district court to address in the first instance on remand, if it remains contested. But the resolution of that issue may be determinative in resolving the parties' dispute about the scope of the injunction.

If Avadel's submission of its paper NDA for Lumryz—for the treatment of IH or any other indication—is an act of infringement under § 271(e)(2), then the district court's injunction barring Avadel from seeking FDA approval of any new indications of Lumryz was unlawful. That is because the injunction exceeds the scope of the limited remedies available to a patent owner for that artificial act of infringement. Specifically, under § 271(e)(4), "the only remedies" that would be available are: (1) an order setting the effective date of any FDA approval of Lumryz to be no sooner than February 18, 2036, the expiration date of the '782 patent; (2) an injunction preventing Avadel's *commercial* activities relating to Lumryz; and (3) damages for any of Avadel's past commercial activities relating to Lumryz. § 271(e)(4)(A)–(C).[9] None of those remedies permits a court to enjoin an adjudicated infringer from applying for additional FDA approvals of a patented drug. To conclude otherwise would run afoul of not only the text of the statute, but also the precise purpose of the Hatch-Waxman Act to encourage "immediate competition" upon expiration of relevant patents. H.R. Rep. No. 98-857, at 46. If Avadel cannot apply for approval of Lumryz until after the '782 patent expires, Jazz will receive a *de facto* extension of patent term to which it is not otherwise entitled for the amount of time it takes the FDA to consider and grant that application. *See Eli Lilly*, 496 U.S. at 676.

If, however, Avadel's submission of its paper NDA is *not* an act of infringement under § 271(e)(2), then the remedies available to Jazz are no longer limited by § 271(e)(4). In that case, it was not improper for the district court to

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[9] The fourth remedy specified in § 271(e)(4)(D) applies only to certain cases involving the Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111–148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010). Accordingly, it is not relevant here.

consider whether enjoining Lumryz from engaging in that activity was warranted based on a full consideration of the *eBay* factors. However, because that activity would not constitute infringement—under either § 271(e)(2) or § 271(a)—to properly enjoin that activity, the district court must have concluded that the injunction was *necessary* to prevent infringement. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1367 (Fed. Cir. 1998) (explaining that an injunction may reach non-infringing activities, but that "[i]t is necessary . . . that the injunction *prevent infringement*" of a patent); *accord TiVo Inc.*, 646 F.3d at 890 n.9.

Here, the district court enjoined Avadel from seeking FDA approval of new indications because it found that "Lumryz's entrance into the IH market would undoubtedly cause Jazz to suffer significant injury." *Decision*, at *10. Unlike the narcolepsy indication, the district court explained, "Jazz's Xywav is the only FDA-approved treatment for IH," and therefore, "Avadel's entrance into the market would strip Jazz of a unique selling point critical to growing its reputation and goodwill." *Id.* That analysis is insufficient to support the injunction at issue here.

It well may be that Jazz would be irreparably harmed upon Lumryz's entrance into the IH market. But entitlement to an injunction requires a showing that there is a "causal nexus" between the alleged irreparable harm and the *enjoined activity*. *See Apple Inc.*, 735 F.3d at 1359–60 (explaining that a patentee must establish "that a sufficiently strong causal nexus relates the alleged harm to the alleged infringement"). Here, the only findings to support enjoining Avadel from seeking FDA approval relate to the harm Jazz would suffer if Avadel were to enter the market for the IH indication—not if Avadel were merely to apply for FDA approval of that indication. Although Avadel's ability to enter the market is, in part, dependent on Avadel seeking FDA approval, it does not follow that enjoining Avadel's application would be *necessary* to prevent infringement. *See Johns Hopkins Univ.*, 152 F.3d at 1367.

Future infringement, *e.g.*, commercialization of Lumryz for IH, can only occur if and when the FDA approves Lumryz for that indication. And any number of things may prevent that approval from ever arriving. Avadel may decide the financial investment in pursuing the approval does not comport with its business prospects. Clinical trials may fail. The district court's analysis is simply too speculative and tenuous to reasonably conclude from its findings that enjoining Avadel from applying for FDA approval is necessary to prevent future infringement.

For those reasons, we vacate the injunction insofar as it bars Avadel from submitting an application for FDA approval of any indication not part of Lumryz's approved product label as of March 4, 2024, and we remand to the district court. On remand, if the issue remains contested, the district court is instructed to consider in the first instance whether Avadel's submission of a paper NDA for an additional indication of Lumryz would be an act of infringement under 35 U.S.C. § 271(e)(2). If so, as discussed above, the district court must conclude that that activity cannot be enjoined. If, however, the district court determines that that submission would not be an act of infringement, the district court must address the *eBay* factors anew in accordance with this opinion before again enjoining that activity.

CONCLUSION

We have considered the parties' remaining arguments and find them unpersuasive. We reverse the injunction to the extent it enjoins Avadel from initiating new clinical trials for Lumryz and from offering OLE periods to current clinical trial participants. We vacate the injunction to the extent it enjoins Avadel from seeking FDA approval for new indications of Lumryz, and remand to the district court for reconsideration of that issue in light of this opinion.

REVERSED-IN-PART, VACATED-IN-PART, AND REMANDED

COSTS

The parties shall bear their own costs.