United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,
Plaintiff-Appellee

v.

HOSPIRA, INC.,
Defendant-Appellant

2018-2126, 2018-2127

Appeals from the United States District Court for the Southern District of Indiana in No. 1:16-cv-03460-TWP-MPB, Judge Tanya Walton Pratt.

ELI LILLY AND COMPANY,
Plaintiff-Appellee

v.

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC.,
Defendants-Appellants

2018-2128

Appeal from the United States District Court for the Southern District of Indiana in No. 1:16-cv-00308-TWP-MPB, Judge Tanya Walton Pratt.

Decided: August 9, 2019

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

LOURIE, *Circuit Judge*.

Hospira Inc. ("Hospira"), Dr. Reddy's Laboratories Ltd., and Dr. Reddy's Laboratories Inc. (collectively, "DRL") appeal from two judgments of the United States District Court for the Southern District of Indiana in two infringement suits brought by Eli Lilly & Company ("Lilly") under the Hatch-Waxman Act, 21 U.S.C. § 355. The district court held in each case that the defendant's submission of a New Drug Application pursuant to 21 U.S.C. § 355(b)(2) infringed U.S. Patent 7,772,209 (the "'209 patent") under 35 U.S.C. § 271(e)(2). *See Eli Lilly & Co. v. Hospira, Inc.*, No. 1:16-cv-03460-TWP-MPB, 2018 WL 3008570 (S.D. Ind. June 15, 2018) ("*Hospira Decision*"); *Eli Lilly & Co. v. Dr. Reddy's Labs., Ltd.*, 323 F. Supp. 3d 1042 (S.D. Ind. 2018) ("*DRL Decision*"); *see also Eli Lilly & Co. v. Dr. Reddy's Labs., Ltd.*, No. 1:16-cv-00308-TWP-MPB, 2017 WL 6387316 (S.D. Ind. Dec. 14, 2017) ("*DRL Summary Judgment Decision*"). Accordingly, the district court entered orders under 35 U.S.C. § 271(e)(4)(A) prohibiting FDA approval of the products at issue until the expiration of the '209 patent. *Eli Lilly & Co. v. Hospira, Inc.*, No. 1:16-cv-03460-TWP-MPB (S.D. Ind. June 27, 2018), ECF No. 94; *Eli Lilly & Co. v. Dr. Reddy's Labs., Ltd.*, No. 1:16-cv-00308-TWP-MPB, 2018 WL 3616715 (S.D. Ind. July 27, 2018). We decide these appeals together in this combined opinion.[1]

We reverse the district court's finding of literal infringement in the *Hospira Decision* as clearly erroneous in light of the court's claim construction of "administration of pemetrexed disodium." Because the district court did not err in its application of the doctrine of equivalents in either

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[1] We refer to the joint appendices in these appeals by reference to each appellant. Lilly's brief in the Hospira appeal is referred to as "Lilly Br. I" and its brief in the DRL appeal as "Lilly Br. II."

decision, we affirm both judgments of infringement. Thus, the *Hospira Decision* is affirmed-in-part and reversed-in-part, and the *DRL Decision* is affirmed.

BACKGROUND

Lilly markets the compound pemetrexed in the form of a disodium salt as Alimta®, which is indicated, both alone and in combination with other active agents, for treating certain types of non-small cell lung cancer and mesothelioma. Pemetrexed is an antifolate, a class of molecules which, at the time of the invention in 2001, was "one of the most thoroughly studied classes of antineoplastic agents." '209 patent col. 1 ll. 19–20. Antifolates are structurally similar to folic acid and work by competitively binding to certain enzymes that use folic acid metabolites as cofactors in several steps of de novo nucleotide synthesis. *Id.* col. 1 ll. 40–41. Unlike folic acid, antifolates do not enable these synthetic steps, but instead inhibit them. Pemetrexed inhibits several of these enzymes, including thymidylate synthase, which methylates deoxyuridine in the final step of deoxythymidine synthesis. *Id.* col. 1 ll. 59–61. By inhibiting the creation of these nucleotides, antifolates slow down DNA and RNA synthesis, and with it, cell growth and division. Cancer cells tend to grow rapidly, so antifolate therapy affects them disproportionately, but healthy cells can also be damaged.

Pemetrexed had been known for at least a decade in 2001. Lilly's U.S. Patent 5,344,932 ("Taylor") disclosed that certain glutamic acid derivatives with pyrrolo[2,3-d]pyrimidine heterocyclic ring structures, exemplified by pemetrexed, are "particularly active . . . inhibitors of thymidylate synth[ase]," Taylor col. 1 ll. 59–60; *see also id.* col. 19 l. 37–col. 20 l. 25 (disclosing data indicating that pemetrexed inhibits thymidylate synthase activity in vitro in human cell lines and in vivo in mice). The Taylor patent also disclosed that its compounds could be employed as "pharmaceutically acceptable salt[s]," *id.* col. 2 l. 35, and

that the disodium salt form was particularly advantageous, *id.* col. 2 ll. 47–48. U.S. Patent 4,997,838 ("Akimoto"), to which Lilly took a license, disclosed a large genus of compounds containing pyrrolo[2,3-d]pyrimidine heterocyclic ring structures and a glutamic acid functional group, and that encompassed pemetrexed. The Akimoto patent discloses nearly fifty exemplary compounds, col. 14 l. 61–col. 16 l. 48, none of which is pemetrexed. Akimoto further discloses that its compounds may be prepared as salts of "pharmaceutically acceptable bases," such as "alkali metals, alkali earth metals, non-toxic metals, ammonium, and substituted ammonium." *Id.* col. 14 ll. 44–47.

By 2001, Lilly had also published the results of several clinical trials investigating the use of pemetrexed disodium as a treatment for different types of cancer. *See, e.g.*, W. John et al., "Activity of Multitargeted Antifolate (Pemetrexed Disodium, LY231514) in Patients with Advanced Colorectal Carcinoma: Results from a Phase II Study," *Cancer*, 88(8):1807–13 (2000). In the course of conducting these studies, Lilly discovered that pemetrexed disodium caused severe hematologic and immunologic side effects, resulting in infections, nausea, rashes, and even some deaths. *See id.*; *see also Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377–78 (Fed. Cir. 2019) (discussing Lilly's response to adverse clinical data), *and Neptune Generics, LLC v. Eli Lilly & Co.*, No. IPR2016-00240, 2017 WL 4466557, at *28–30 (P.T.A.B. Oct. 5, 2017) (same). As the '209 patent teaches, such side effects are not uncommon among antifolates. *See* '209 patent col. 1 ll. 11–14. Some researchers hypothesized that folic acid deficiency caused these side effects and suggested supplementing pemetrexed disodium treatment with folic acid. DRL J.A. 7870 (citing J.F. Worzalla et al., "Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514," *Anticancer Research*, 18:3235–40 (1998)).

The invention of the '209 patent is an improved method of treatment with antifolates, particularly pemetrexed disodium, through supplementation with a methylmalonic acid lowering agent and folic acid. Doing so, according to the patent, lessens antifolate toxicity without sacrificing efficacy. *See* '209 patent col. 10 ll. 17–53 (reporting that pre-supplementation regimen of vitamin B12 and folic acid in clinical studies substantially reduced pemetrexed-induced toxicity and deaths while delivering a superior chemotherapeutic response rate). The '209 patent lists preferred antifolates, including some then-existing antifolate therapies, as well as "derivatives described in" several patents including the Akimoto patent, and "most preferred, Pemetrexed Disodium." *Id.* col. 4 ll. 28–43. Each of the claims of the '209 patent requires administration of pemetrexed disodium following administration of folic acid and a methylmalonic acid lowering agent, specified in some claims, as well as the Alimta® label, as vitamin B12. Claim 12 is representative[2]:

> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
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> > a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;

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[2] The district court treated claim 12 as representative, *DRL Summary Judgment Decision*, 2017 WL 6387316, at *1–2; *Hospira Decision*, 2018 WL 3008570, at *2, and no party has disputed that determination on appeal. *See, e.g.*, DRL Opening Br. 8–9; Hospira Opening Br. 23.

> b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

In a parent application, Application 10/297,821 (the "'821 application"), Lilly originally sought broad claims to methods of administering an antifolate in conjunction with a methylmalonic acid lowering agent, with or without folic acid. The original independent claims 2 and 5 read:

> 2. (Original) A method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising
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> > administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.
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> 5. (Original) A method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising
>
> > administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and FBP binding agent.

DRL J.A. 7860. A dependent claim further limited the antifolate to pemetrexed disodium. *Id.* at 7861.

Claim 2 was rejected as anticipated by F.G. Arsenyan et al., "Influence of Methylcobalamin on the Antineoplastic Activity of Methotrexate," *Onkol. Nauchn.*, 12(10):1299-1303 (1978), which disclosed experiments treating mice with various tumors with a combination of methotrexate, an antifolate, and methylcobalamin, a vitamin B12 derivative. The rest of the pending claims, including Claim 5, were rejected as obvious over a collection of references: U.S. Patent 5,431,925 ("Ohmori")—which taught treatment of

chemotherapeutically-induced immunosuppression with a combination of vitamins that could include folic acid and vitamin B12—Worzalla, John, and Arsenyan. '821 application, Sept. 27, 2004, Office Action; DRL J.A. 7868–72.

In response, Lilly amended both claims to narrow "antifolate" to "pemetrexed disodium" and cancelled its dependent claim limited to pemetrexed disodium. '821 application, Jan. 25, 2005, Response to Office Action; DRL J.A. 7877–84. In its remarks, Lilly asserted that the amendment to claim 2 overcame the anticipation rejection because Arsenyan does not disclose pemetrexed disodium. *Id.* To overcome the obviousness rejection of claim 5 and its dependents, Lilly generally argued that, while John discloses hematologic and immunologic toxicities from administration of pemetrexed disodium, it never suggests vitamin supplementation, and none of the other references "teach the use of [vitamin B12] to reduce toxicities associated with an antifolate." *Id.* The examiner then withdrew the anticipation rejection and later withdrew the obviousness rejection. The '821 application issued as U.S. Patent 7,053,065, and the '209 patent later issued from a continuation application.

These appeals were taken from cases which are among the latest in a series of patent disputes about Alimta® that reaches back more than a decade.[3] In this most recent chapter, DRL, Hospira, and Actavis[4] submitted New Drug

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[3] This is the fourth appeal we have decided concerning Alimta® and the third specifically concerning the '209 patent. *See Neptune Generics*, 921 F.3d 1372; *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357 (Fed. Cir. 2017); *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368 (Fed. Cir. 2012).

[4] Lilly also sued Actavis LLC ("Actavis") for infringement of the '209 patent, *Eli Lilly & Co. v. Actavis LLC*, No. 1:17-cv-00982-TWP-MPB (S.D. Ind. Mar. 30, 2017), ECF

Applications under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(2), relying on Lilly's clinical data for pemetrexed disodium. But each applicant seeks to market different pemetrexed salts—in DRL's and Hospira's applications, pemetrexed ditromethamine. Both DRL and Hospira represented to the FDA that their choice of the tromethamine cation was immaterial because pemetrexed dissociates from its counterion in solution, DRL J.A. 8555–57; Hospira J.A. 124, and tromethamine was known to be safe for pharmaceutical use, DRL J.A. 8555, 8557.

Lilly then asserted the '209 patent against each of these NDA applicants in the United States District Court for the Southern District of Indiana. In the DRL case, the district court construed the phrase "administration of pemetrexed disodium" to mean "liquid administration of pemetrexed disodium," which "is accomplished by dissolving the solid compound pemetrexed disodium into solution." *DRL Summary Judgment Decision*, 2017 WL 6387316, at *4. The district court denied DRL's motion for summary judgment of noninfringement, holding that prosecution history estoppel does not bar Lilly from asserting that DRL's proposed pemetrexed ditromethamine product would infringe through the doctrine of equivalents because the reason for Lilly's amendment was to distinguish other antifolates and was therefore only tangential to pemetrexed ditromethamine. *Id.* at *6–7. The district court also rejected DRL's argument that Lilly dedicated

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No. 1, but the parties stipulated to be bound by the district court's decision in the DRL case that neither prosecution history estoppel nor the disclosure-dedication rule bars Lilly's assertion of infringement through the doctrine of equivalents. Actavis Br. 2. Actavis filed a brief in the DRL appeal as amicus curiae requesting reversal of that portion of the district court's decision.

pemetrexed ditromethamine to the public under the disclosure-dedication rule through its reference to Akimoto's antifolate compounds because Akimoto is not incorporated by reference into the '209 patent and in any event discloses pemetrexed ditromethamine only within a genus of thousands of compounds, which the district court held does not constitute the requisite disclosure of an identifiable alternative under this court's precedent. *Id.* at *7–8; *see, e.g.*, *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1363 (Fed. Cir. 2012).

Following a bench trial, the district court's opinion largely followed its rationale in the *DRL Summary Judgment Decision* with respect to the applicability of prosecution history estoppel and the disclosure-dedication rule. *DRL Decision*, 323 F. Supp. 3d at 1046–48. In addition, the court found that DRL's proposed product would be administered in a manner that would meet the "administration of pemetrexed disodium" step of the asserted claims under the doctrine of equivalents, *id.* at 1049, regardless of the "differences in chemical properties between pemetrexed disodium and pemetrexed ditromethamine," *id.* at 1050.

In the Hospira case, the parties similarly disputed the doctrine of equivalents, but Lilly also asserted literal infringement because Hospira's proposed product label allows reconstitution of its pemetrexed ditromethamine salt in saline. *Hospira Decision*, 2018 WL 3008570, at *2–3; Hospira J.A. 229. After the district court issued the *DRL Summary Judgment Decision*, Hospira conceded, contingent upon its right to appeal, that its product would infringe under the claim construction of "administration of pemetrexed disodium" set forth in that opinion and that its doctrine of equivalents arguments were likewise foreclosed. Hospira Br. 18. The district court, "rel[ying] heavily" on the *DRL Summary Judgment Decision*, granted Lilly's motion for summary judgment of infringement, both literally and under the doctrine of equivalents. *Hospira Decision*, 2018 WL 3008570, at *1 n.2, *6.

These appeals followed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a district court's grant of summary judgment according to the law of the regional circuit. *Kaneka Corp. v. Xiamen Kingdomway Grp. Co.*, 790 F.3d 1298, 1303 (Fed. Cir. 2015) (citing *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 769 F.3d 1371, 1377 (Fed. Cir. 2014)). In the Seventh Circuit, summary judgment is reviewed *de novo*, construing all facts and drawing all inferences in favor of the non-movant. *Wis. Alumni Research Found. v. Apple Inc.*, 905 F.3d 1341, 1352 (Fed. Cir. 2018) (citing *Austin v. Walgreen Co.*, 885 F.3d 1085, 1087 (7th Cir. 2018)). On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1358 (Fed. Cir. 2014) (citing *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1123 (Fed. Cir. 2000)). A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

Claim construction is ultimately an issue of law, which we review *de novo*. *Shire Dev., LLC v. Watson Pharm., Inc.*, 787 F.3d 1359, 1364 (Fed. Cir. 2015). We review *de novo* the district court's findings of fact on evidence "intrinsic to the patent (the patent claims and specification[], along with the patent's prosecution history)," and review for clear error extrinsic findings of fact. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). While infringement is a question of fact, *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1309 (Fed. Cir. 2009), we review *de novo* the district court's grant of summary judgment of non-infringement, *Unwired Planet, LLC v. Apple Inc.*, 829 F.3d 1353, 1356 (Fed. Cir. 2016). To prove infringement, a patentee "must supply sufficient evidence to prove that the

accused product or process contains, either literally or under the doctrine of equivalents, every limitation of the properly construed claim." *Seal-Flex, Inc. v. Athletic Track & Court Const.*, 172 F.3d 836, 842 (Fed. Cir. 1999). The patentee has the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

Hospira requests reversal of the district court's finding that its submission of a § 505(b)(2) NDA for its pemetrexed product literally infringed the claims of the '209 patent. DRL and Hospira both argue, as does the amicus curiae Actavis, that the district court erred as a matter of law by refusing to apply prosecution history estoppel to bar Lilly's doctrine of equivalents claim, and DRL further contends that the disclosure-dedication rule precludes Lilly's equivalents claim. Finally, DRL disputes the district court's finding that administration of pemetrexed ditromethamine is equivalent to the claim element "administration of pemetrexed disodium." We address each argument in turn.

A. Literal Infringement

Hospira argues that it cannot literally infringe the claims of the '209 patent because intravenous administration of pemetrexed ditromethamine dissolved in saline—a solution which contains pemetrexed and chloride anions alongside sodium and tromethamine cations—is not "administration of pemetrexed disodium." Hospira also notes that such a solution will, in any case, contain far more than two sodium cations per pemetrexed anion. Finally, Hospira appears to make a perfunctory argument that, in the alternative, we should reverse the district court's construction and hold that the term encompasses any route of administering pemetrexed disodium, not just liquid, as the district court's construction requires.

Lilly counters that Hospira's view improperly imposes a "source limitation," requiring that the pemetrexed disodium salt exist in solid form before administration, even

though Hospira's proposed product label, like that of Alimta®, calls for administration of a solution containing pemetrexed anions and sodium cations. Lilly also contends that Hospira's claim construction arguments are irrelevant because Hospira's proposed product will be administered intravenously anyway.

We agree with Hospira. It was clearly erroneous for the district court to hold that the "administration of pemetrexed disodium" step was met because Hospira's pemetrexed ditromethamine product will be dissolved in saline before administration. A solution of pemetrexed and chloride anions and tromethamine and sodium cations cannot be deemed pemetrexed disodium simply because some assortment of the ions in the solution consists of pemetrexed and two sodium cations. As Lilly acknowledges throughout its brief, pemetrexed disodium is a salt. *See, e.g.*, Lilly Br. I 12 (pemetrexed toxicity is caused "by pemetrexed itself once dissociated in solution," not pemetrexed disodium); *see also* Hospira J.A. 1596 (October 2017 Alimta® Label referring to the drug substance as the "disodium salt" of pemetrexed). Once diluted, the salt's crystalline structure dissolves, and the individual ions dissociate. *See* Hospira J.A. 2820 (declaration of Lilly's expert). In other words, pemetrexed disodium no longer exists once dissolved in solution, and, as a corollary, a different salt of pemetrexed dissolved in saline is not pemetrexed disodium.

We conclude that to literally practice the "administration of pemetrexed disodium" step under the district court's claim construction, the pemetrexed disodium salt must be itself administered. *See DRL Summary Judgment Decision*, 2017 WL 6387316, at *4 ("'[A]dministration of pemetrexed disodium' . . . refer[s] to a liquid administration of pemetrexed disodium. . . ., accomplished by dissolving the solid compound pemetrexed disodium into solution . . . ."); *see also Tex. Instruments Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1563 (Fed. Cir. 1996) ("To

literally infringe, the accused . . . process must contain every limitation of the asserted claim." (citing *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991))). There is no dispute that Hospira has only sought approval to market pemetrexed ditromethamine, Lilly Br. I 4, and that neither its proposed product nor methods of administering it will constitute administering the pemetrexed disodium salt. Accordingly, Hospira will not practice the step of "administration of pemetrexed disodium," and the district court's finding of literal infringement must be reversed.

B. Doctrine of Equivalents

Few propositions of patent law have been so consistently sustained by the Supreme Court as the doctrine of equivalents. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushki Co.*, 535 U.S. 722, 733 (2002) ("*Festo VIII*") ("[E]quivalents remain a firmly entrenched part of the settled rights protected by the patent."); *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997) ("[W]e adhere to the doctrine of equivalents."); *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950) ("Originating almost a century ago in the case of *Winans v. Denmead*, [56 U.S. 330 (1853)] . . . [the doctrine of equivalents] has been consistently applied by this Court and the lower federal courts, and continues today ready and available for utilization when the proper circumstances for its application arise."). It is settled that a patentee is entitled "in all cases to invoke to some extent the doctrine of equivalents," *Seymour v. Osborne*, 78 U.S. 516, 555 (1870), without a "judicial exploration of the equities of a case" beforehand. *See Warner-Jenkinson*, 520 U.S. at 34.

Yet the Supreme Court has also acknowledged that the doctrine of equivalents, "when applied broadly, conflicts with the definitional and public-notice functions of the statutory claiming requirement," *Warner-Jenkinson*, 520 U.S. at 29, and that, without the proper balance between these

two imperatives, the doctrine may "take[] on a life of its own, unbounded by the patent claims." *See id.* at 28–29. We have emphasized, moreover, that the doctrine of equivalents is "the exception, however, not the rule," and not merely "the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims." *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538 (Fed. Cir. 1991). Patent infringement is principally determined by examining whether the accused subject matter falls within the scope of the claims.

To that end, courts have placed important limitations on a patentee's ability to assert infringement under the doctrine of equivalents. *See, e.g.*, *Festo VIII*, 535 U.S. at 737–41 (prosecution history estoppel); *Warner-Jenkinson*, 520 U.S. at 39 n.8 ("[A] theory of equivalence [cannot] entirely vitiate a particular claim element . . . ."); *Graver Tank*, 339 U.S. at 608 (accused equivalent cannot differ substantially from the claimed invention); *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002) (en banc) (subject matter disclosed but not claimed is dedicated to the public) (citing *Maxwell v. J. Baker, Inc.*, 86 F.3d 1098 (Fed. Cir. 1996)); *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 683 (Fed. Cir. 1990) ("[T]he asserted scope of equivalency [cannot] encompass the prior art . . . ." (Rich, J.) (citations omitted)). These appeals implicate several of these limitations.

1. Prosecution History Estoppel

The main dispute in these appeals is whether Lilly has rebutted the presumption of prosecution history estoppel that attached to its amendment in the '821 application. Prosecution history estoppel arises when a patent applicant narrows the scope of his claims during prosecution for a reason "substantial[ly] relating to patentability." *See generally Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1366–67 (Fed. Cir. 2003) (en banc) ("*Festo X*"). Such a narrowing amendment is presumed to

be a surrender of all equivalents within "the territory between the original claim and the amended claim," but the presumption is overcome if the patentee can show the applicability of one of the few exceptions identified by the Supreme Court. *Festo VIII*, 535 U.S. at 740–41 (citing *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126, 136–37 (1942)). Whether prosecution history estoppel applies to bar a doctrine of equivalents claim is a question of law, reviewed *de novo*. *See Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1371 (Fed. Cir. 2008) (citing *Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1376 (Fed. Cir. 1999)).

Lilly does not dispute that the amendment in question was both narrowing and made for a substantial reason relating to patentability. Lilly Br. II 21. Furthermore, Lilly relies on only one exception to giving effect to the presumption as to the scope of surrender: that the rationale of its amendment "[bore] no more than a tangential relation to the equivalent in question." *Festo VIII*, 535 U.S. at 740. As a result, the parties' dispute about whether prosecution history estoppel applies is confined to whether Lilly's amendment narrowing "an antifolate" to "pemetrexed disodium" was only tangential to pemetrexed ditromethamine, which is the accused compound. Whether the tangential exception applies is a question of law, *Integrated Tech. Corp. v. Rudolph Techs., Inc.*, 734 F.3d 1352, 1356 (Fed. Cir. 2013), and a patentee seeking to use the exception "must base his arguments solely upon the public record of the patent's prosecution." *Festo X*, 344 F.3d at 1369–70 (citation omitted).

The Appellants argue that Lilly failed to explain why it did not pursue a narrower amendment literally encompassing pemetrexed ditromethamine, and they emphasize our statement that the tangential exception is "very narrow." *Integrated*, 734 F.3d at 1358 (quoting *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 480 F.3d 1335, 1342 (Fed. Cir. 2007)). The Appellants further point

out that Lilly cannot be said to have "lacked the words to describe" pemetrexed ditromethamine, *see Festo VIII*, 535 U.S. at 734, because Lilly's previous patents, as well as the European companion to the '209 patent, claimed pemetrexed salts generally and pemetrexed disodium in a dependent claim. They also assert that the district court erred by focusing on whether Lilly actually needed to relinquish pemetrexed ditromethamine to overcome the Arsenyan anticipation rejection because "the tangential exception is not a patentee's-buyer's-remorse exception." DRL Br. 39.

In response, Lilly argues that the district court properly held that the reason for its amendment was to distinguish pemetrexed from antifolates generally and that the different salt type is a merely tangential change with no consequence for pemetrexed's administration or mechanism of action within the body. Lilly also contends that it is not barred from asserting the tangential exception simply because pemetrexed ditromethamine is within "the territory between the original claim and the amended claim." *Festo VIII*, 535 U.S. at 740. Finally, Lilly argues that Appellants' view that courts must "consider hypothetical alternative amendments" that would literally encompass the alleged equivalent "would eviscerate the tangentiality exception." Lilly Br. II 44.

We agree with Lilly. As a general matter, we find Appellants' view of prosecution history estoppel, and the tangential exception in particular, too rigid. Tangential means "touching lightly or in the most tenuous way." Webster's Third New International Dictionary (2002). The reason for Lilly's amendment, as the district court concluded, was to narrow original claim 2 to avoid Arsenyan, which only discloses treatments using methotrexate, a different antifolate. *See* DRL J.A. 7879–80 (overcoming the Arsenyan anticipation rejection by arguing that it "does not disclose pemetrexed disodium"). To overcome a clear anticipation, Lilly opted to narrow its original claim 2 and

its dependents to more accurately define what it actually invented, an improved method of administering pemetrexed. In other words, the particular type of salt to which pemetrexed is complexed relates only tenuously to the reason for the narrowing amendment, which was to avoid Arsenyan. We therefore hold that Lilly's amendment was merely tangential to pemetrexed ditromethamine because the prosecution history, in view of the '209 patent itself, strongly indicates that the reason for the amendment was not to cede other, functionally identical, pemetrexed salts.

The prosecution record confirms our understanding. Original claim 5, which, like all the current claims of the '209 patent, required supplementation with both vitamin B12 and folic acid, was never rejected as anticipated over Arsenyan. Instead, the art cited against original claim 5 and its dependent claims in the obviousness ground of rejection was replete with information about pemetrexed disodium; John disclosed clinical trials using pemetrexed disodium, reporting both its efficacy and its toxic side effects, and in response, DRL J.A. 7869–70, Worzalla suggested folic acid supplementation to counteract these side effects, DRL J.A. 7870–71. The prosecution record implies that Lilly's amendment, inartful though it might have been, was prudential in nature and did not need or intend to cede other pemetrexed salts.

Hospira argues that the amendment was made to overcome the obviousness rejection over Ohmori and John and that Lilly has provided no reason for the amendment relative to that rejection. Like Lilly, we find this argument makes little sense. John discloses the results of a clinical trial of pemetrexed disodium and explicitly suggests the toxicities caused by pemetrexed; as we concluded above, narrowing "antifolate" to "pemetrexed disodium" could not possibly distinguish the art cited in the obviousness ground of rejection.

DRL also insists that we have held that an applicant's remorse at ceding more claim scope than necessary is not a reason for the tangential exception to apply. *See, e.g.*, *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1218 (Fed. Cir. 2008); *Schwarz Pharma, Inc. v. Paddock Labs., Inc.*, 504 F.3d 1371, 1377 (Fed. Cir. 2007). This is generally true, but DRL overreads the holdings of these cases. After all, the tangential exception only exists because applicants over-narrow their claims during prosecution. Amendments are not construed to cede only that which is necessary to overcome the prior art, *see Schwarz*, 504 F.3d at 1377, nor will the court "speculat[e]" whether an amendment was necessary, *see Kinzenbaw v. Deere & Co.*, 741 F.2d 383, 389 (Fed. Cir. 1984). But the reason for an amendment, where the tangential exception is invoked, cannot be determined without reference to the context in which it was made, including the prior art that might have given rise to the amendment in the first place. *See Festo X*, 344 F.3d at 1370. Here, it is unlikely that a competitor would have been "justified in assuming that if he [made an equivalent pemetrexed salt], he would not infringe [the '209 patent]." *Kinzenbaw*, 741 F.2d at 389; *cf. Festo VIII*, 535 U.S. at 738 ("There is no reason why a narrowing amendment should be deemed to relinquish equivalents . . . beyond a fair interpretation of what was surrendered.").

Furthermore, Appellants' suggestion that Lilly must prove that it could not have drafted a claim that literally encompassed pemetrexed ditromethamine is unsupported by our precedent on prosecution history estoppel, not to mention excessive. We do not demand perfection from patent prosecutors, and neither does the Supreme Court. *See Festo VIII*, 535 U.S. at 738 ("It does not follow . . . that [an] amended claim becomes so perfect in its description that no one could devise an equivalent."). Lilly's burden was to show that pemetrexed ditromethamine was "peripheral, or not directly relevant," to its amendment, *Festo X*, 344 F.3d at 1369. And as we concluded above, Lilly has done so.

In addition, the Appellants maintain that when a patentee submits an amendment adding two claim limitations, it cannot later argue that the reason for the amendment was tangential to an accused equivalent containing only one of the added limitations simply because the second limitation was unnecessary to overcome the prior art. They offer *Felix v. American Honda Motor Co.*, 562 F.3d 1167 (Fed. Cir. 2009), as an illustration of this principle.[5] In that case, we held that prosecution history estoppel applied to a claim directed to a vehicle bed storage system—limited in response to a rejection to having a channel with a flange and a gasket mounted on that flange—barring assertion of equivalence with respect to a product that met the channel aspect, but not the gasket aspect, of the limitation. *Id.* at 1184–85.

But as Lilly points out, this holding was determined by that patent's prosecution history, *Felix*, 562 F.3d at 1184, and we have also held that prosecution history estoppel does not apply in similar circumstances, where the

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[5] The parties argue at length about which of our cases are properly analogous to the facts presented in these appeals. Here, in applying the Supreme Court's framework, we find the analogies to other cases less helpful than a direct consideration of the specific record of this case and what it shows about the reason for amendment and the relation of that reason to the asserted equivalent. This case-specific focus, within the governing framework, comports with the equitable nature of prosecution history estoppel. *See Festo VIII*, 535 U.S. at 738 ("[The Supreme Court has] consistently applied the doctrine in a flexible way, not a rigid one."); *cf. Heckler v. Cmty. Health Servs. of Crawford Cty., Inc.*, 467 U.S. 51, 59 (1984) ("Estoppel is an equitable doctrine invoked to avoid injustice in particular cases. . . . [and] a hallmark of the doctrine is its flexible application . . . .").

prosecution record differed. *See, e.g.*, *Regents*, 517 F.3d at 1376–78 (amendment narrowing "disabling hybridization capacity of [nucleic acid] sequences" to methods using a "blocking nucleic acid" was merely tangential to unclaimed repetitive sequence nucleic acids); *Insituform Techs., Inc. v. CAT Contracting, Inc.*, 385 F.3d 1360, 1368 (Fed. Cir. 2004) (amendment narrowing method of inserting resin into tube using a vacuum to one using "a cup" to do so was merely tangential to a multiple cup embodiment because the number of cups bore no relationship to the cited prior art or the rationale behind the narrowing amendment). Thus, our cases demonstrate that prosecution history estoppel is resistant to the rigid legal formulae that Appellants seek to extract from them. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1291 (Fed. Cir. 2010) ("[T]here is no hard-and-fast test for what is and what is not a tangential relation . . . .").

Finally, DRL also contends that our precedent squarely forecloses Lilly's tangentiality argument, and it invites us to read those cases to hold that "where the reason for the amendment and the equivalent in question both relate to the same claim element, the tangential exception does not apply." DRL Br. 47. We decline this invitation because such a bright-line rule is both contrary to the equitable nature of prosecution history estoppel, as articulated in *Festo VIII*, 535 U.S. at 738, and inconsistent with the equitable spirit that animates the doctrine of equivalents, *see Graver Tank*, 339 U.S. at 608–09 (the doctrine is one of "wholesome realism"). Instead, we reaffirm that whether an amendment was merely tangential to an equivalent must be decided in the context of the invention disclosed in the patent and the prosecution history. *Festo X*, 344 F.3d at 1370.

DRL's intuition—that an amendment that narrows an existing claim element evinces an intention to relinquish that claim scope—is often correct. Indeed, as we have found in previous cases, it is a powerful indication that an

amendment was not merely tangential. *See, e.g.*, *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1315–16 (Fed. Cir. 2008); *Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1306 (Fed. Cir. 2005). But here, we conclude that this consideration is not dispositive because the rest of the prosecution history, and the '209 patent itself, show that it is implausible that the reason for Lilly's amendment was to surrender other pemetrexed salts. Indeed, such a relinquishment would effectively dedicate the entirety of Lilly's invention to the public and thereby render the '209 patent worthless, and it would have been irrelevant for distinguishing the prior art. Again, the prosecution history strongly indicates a less sweeping and more sensible reason for Lilly's amendment: to surrender antifolates other than pemetrexed. Thus, we conclude on this prosecution record that Lilly's amendment was merely tangential to pemetrexed ditromethamine.

2. Disclosure-Dedication Rule

DRL next argues that the disclosure-dedication rule bars Lilly from asserting infringement under the doctrine of equivalents. The '209 patent sets forth its invention as an improved method of administering antifolates, '209 patent col. 2 ll. 47–58, and teaches that the derivatives described in the Akimoto patent are preferred examples of antifolates, *id.* col. 4 ll. 34–40. DRL contends that one of these derivatives is pemetrexed ditromethamine and that it was dedicated to the public when Lilly declined to claim it. DRL asserts that the district court erred because it both required express incorporation of Akimoto by reference into the '209 patent and concluded that Akimoto does not specifically disclose pemetrexed ditromethamine.

Lilly counters that the disclosure-dedication rule requires express disclosure of the subject matter in question in the specification except in narrow circumstances, such as when that subject matter is disclosed in a priority application, *see Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282,

1297 (Fed. Cir. 2009), or prior art expressly incorporated by reference, *SanDisk*, 695 F.3d at 1366. Lilly also argues that the district court correctly determined that the relevant portion of Akimoto discloses only a generic formula from which a skilled artisan would not be able to recognize pemetrexed ditromethamine.

We agree with Lilly and hold that the disclosure-dedication rule is inapplicable to this case because the '209 patent does not disclose methods of treatment using pemetrexed ditromethamine, and, as a result, Lilly could not have dedicated such a method to the public.

Under the disclosure-dedication rule, subject matter disclosed by a patentee, but not claimed, is considered dedicated to the public. *See Johnson & Johnston*, 285 F.3d at 1054. The reason for the doctrine is that members of the public reading a disclosure of particular subject matter are entitled, absent a claim to it, to assume that it is not patented and therefore dedicated to the public (unless, for example, claimed in a continuation or other application based on the disclosure). *Cf. Maxwell*, 86 F.3d at 1107 (failure to claim inventive subject matter "is clearly contrary to 35 U.S.C. § 112, which requires that a patent applicant 'particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention'"). Subject matter is considered disclosed when a skilled artisan "can understand the unclaimed disclosed teaching upon reading the written description," but not "any generic reference . . . necessarily dedicates all members of that particular genus." *PSC Comput. Prod., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1360 (Fed. Cir. 2004).

DRL further contends that the disclosure-dedication rule does not impose a § 112 requirement for sufficiency of disclosure, *see Toro Co. v. White Consol. Indus., Inc.*, 383 F.3d 1326, 1334 (Fed. Cir. 2004), and that a skilled artisan reading the '209 patent would both look for a disclosure of pemetrexed in Akimoto, and also seek to use a well-known

cation like tromethamine, which it maintains is generically disclosed in Akimoto in the form of "substituted ammonium" base salts.

We are unpersuaded by DRL's arguments. As the district court noted, Akimoto's formula, col. 1 l. 49–col. 2 l. 3, includes seven functional group variables and encompasses thousands of compounds, and while Akimoto discloses about fifty exemplary compounds, none of them is pemetrexed. Moreover, Akimoto does not even disclose tromethamine expressly but only generically among dozens of other salts. At most, Akimoto discloses ammonium salts generally, which is far from a description of tromethamine. In similar circumstances, we have held that "sufficient description of a genus" requires that a skilled artisan be able to "'visualize or recognize' the members of the genus." *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)). Akimoto does not so describe pemetrexed ditromethamine, and we see no reason why a skilled artisan would set out on DRL's winding path to cobble together pemetrexed ditromethamine. While the '209 patent teaches that pemetrexed disodium is the "most preferred" antifolate, that knowledge would not change the skilled artisan's understanding of what Akimoto discloses.

Because Akimoto contains only a "generic reference" to pemetrexed ditromethamine, *PSC Comput.*, 355 F.3d at 1360, we conclude that it was not dedicated to the public.

3. Merits

A component in an accused product or process may be equivalent to a claim element if the two are insubstantially different with respect to the "role played by [the] element in the context of the specific patent claim." *Warner-Jenkinson*, 520 U.S. at 39–40. Relevant differences can include the function each serves, the way in which each works, and the result each obtains, *id.* at 39, and, especially

in biochemical cases, structural or pharmacological characteristics, *Mylan Inst. LLC v. Aurobindo Pharm. Ltd.*, 857 F.3d 858, 869 (Fed. Cir. 2017). "The determination of equivalency *vel non* is a question of fact," *Canton Bio Med., Inc. v. Integrated Liner Techs., Inc.*, 216 F.3d 1367, 1369 (Fed. Cir. 2000) (citing *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1218 (Fed. Cir. 1995)), which we review for clear error in an appeal from a bench trial, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007).

DRL argues that the district court erred in finding that its proposed pemetrexed ditromethamine product will be administered in an insubstantially different way from the claimed method. DRL maintains that the district court focused on the fact that each product treats the same diseases by delivering pemetrexed intravenously, when the relevant context is the manner of administration. In DRL's view, the chemical differences between sodium and tromethamine—*e.g.*, pH, buffering capacity, or solubility—DRL Br. 20–21, render the methods in which each is administered to a patient substantially different.

Lilly responds that the relevant context is treatment of a patient "in need of chemotherapeutic treatment." '209 patent claim 12. Lilly agrees with the district court that the chemical differences between sodium and tromethamine are clinically irrelevant because each undisputedly lacks therapeutic activity.

We see no clear error in the district court's findings. As the district court found, DRL's product will accomplish an identical aim, furnishing the same amount of pemetrexed to active sites in the body; in exactly the same way, by diluting a pemetrexed salt in an aqueous solution for intravenous administration. Indeed, after dilution and immediately before administration, DRL's product is functionally identical to Lilly's in that it contains the same amount of diluted pemetrexed anion. DRL J.A. 8557. And DRL declines to identify the relevance of any of the

chemical differences it identifies. *See UCB, Inc. v. Watson Labs. Inc.*, 927 F.3d 1272, 1284–86 (Fed. Cir. 2019) (chemical differences may not be relevant if the equivalent has known interchangeability in the context of the claimed composition). We find DRL's arguments unconvincing and therefore affirm the district court's findings.

In summary, these cases are eminently suitable for application of the doctrine of equivalents, and we conclude that neither prosecution history estoppel nor the disclosure-dedication rule bars Lilly from asserting infringement through equivalence.

CONCLUSION

We have fully considered each party's further arguments but find them unpersuasive. For the foregoing reasons, we reverse the district court's finding of literal infringement in the *Hospira Decision* but affirm its judgment of infringement under the doctrine of equivalents. The judgment of infringement under the doctrine of equivalents in the *DRL Decision* is likewise affirmed.

AFFIRMED-IN-PART AND REVERSED-IN-PART IN APPEAL NOS. 2018-2126, 2018-2127

AFFIRMED IN APPEAL NO. 2018-2128

COSTS

Each party shall bear its own costs.