United States Court of Appeals for the Federal Circuit

MYLAN INSTITUTIONAL LLC, APICORE US LLC,
Plaintiffs-Appellees

v.

AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA INC., AUROMEDICS PHARMA LLC,
Defendants-Appellants

2017-1645

Appeal from the United States District Court for the Eastern District of Texas in No. 2:16-cv-00491-RWS-RSP, Judge Robert Schroeder, III.

Decided: May 19, 2017

NICOLE W. STAFFORD, Wilson, Sonsini, Goodrich & Rosati, PC, Austin, TX, argued for plaintiffs-appellees. Plaintiff-appellee Mylan Institutional LLC also represented by DAVID S. STEUER, Palo Alto, CA; SAMI SEDGHANI, San Francisco, CA.

JOANNA GARELICK GOLDSTEIN, Sharma & DeYoung LLP, New York, NY, for Apicore US LLC. Also represented by ALLEN GARDNER, Gillam, Smith & Gardner, Tyler, TX.

SAILESH K. PATEL, Schiff Hardin LLP, Chicago, IL, argued for defendants-appellants. Also represented by CINDY AHN; GEORGE CHIH-LUN YU, San Francisco, CA.

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

LOURIE, *Circuit Judge*.

Aurobindo Pharma Ltd., Aurobindo Pharma USA Inc., and Auromedics Pharma LLC (together, "Aurobindo") appeal from a decision of the United States District Court for the Eastern District of Texas granting Mylan Institutional LLC's ("Mylan Inst.") and Apicore US LLC's ("Apicore") (together, "Mylan") motion for a preliminary injunction precluding Aurobindo from making, using, selling, offering to sell, and importing the accused isosulfan blue ("ISB") product that allegedly infringes three of Apicore's patents—U.S. Patent 7,622,992 ("the '992 patent"), U.S. Patent 8,969,616 ("the '616 patent"), and U.S. Patent 9,353,050 ("the '050 patent"). *See Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, No. 2:16-cv-00491, 2017 WL 497593 (E.D. Tex. Feb. 7, 2017) ("*Order Adopting R&R*"). Because the district court did not err in its grant of the preliminary injunction under the '050 patent, although it did err in granting the injunction under the '992 and '616 patents, we affirm.

BACKGROUND

Apicore owns, and Mylan Inst. is the exclusive licensee of, the '992, '616, and '050 patents, which relate to ISB, a triarylmethane dye used to map lymph nodes. The '992 and '616 patents (together, "the process patents") are directed to a process for preparing ISB by reacting isoleuco acid with silver oxide in a polar solvent, followed by reaction with a sodium solution. *See, e.g.*, '992 patent col.

7 ll. 21–44.[1] The '992 patent further requires 2.0–3.0 equivalents of silver oxide. *See id.* col. 9 l. 65. Claim 1 of the '616 patent is representative of the process patents and reads as follows:

> A process of preparing N-[4-[[4-(diethyl-amino)phenyl] (2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt comprising combining a suspension of isoleuco acid of the formula
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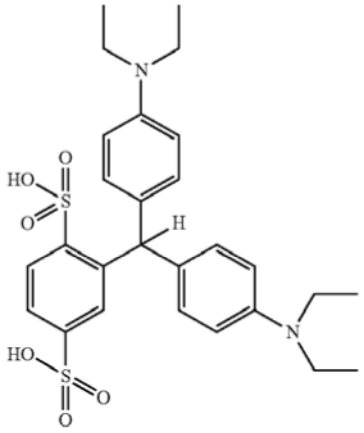
> 
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> in a polar solvent with *silver oxide*, recovering isosulfan blue acid, and treating the isosulfan blue acid with a sodium solution.

'616 patent col. 9 ll. 38–64 (emphasis added). Claim 1 of the '992 patent adds the limitation that 2.0–3.0 equivalents of silver oxide are employed in the process, but otherwise resembles the claim shown above. *See* '992 patent col. 9 ll. 41–67.

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[1] Because the '992, '616, and '050 patents have the same written description, when referring to the written description of any of the patents, we will cite only the '992 patent for simplicity.

The '050 patent (which the parties refer to as "the purity patent") is directed to an ISB compound having a purity greater than 99.0%, as measured by high performance liquid chromatography ("HPLC"). *See* '050 patent col. 9 ll. 54–58. Claim 1 is illustrative and reads as follows:

> A compound N-[4-[[4-(diethylamino)phenyl] (2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt *having a purity of at least 99.0% by HPLC*.

Id. col. 9 ll. 55–58 (emphasis added).

Around 1981, Hirsch Industries ("Hirsch") developed a 1% injectable solution of ISB, which it commercialized under the trade name Lymphazurin®. Covidien Ltd. ("Covidien"), the successor-in-interest to Hirsch, held the original new drug application ("NDA") and was the sole supplier of Lymphazurin® for 30 years. From its inception, Lymphazurin®'s production had been plagued by difficulties in synthesizing and purifying ISB. Hirsch's original clinical trials described the mixture as containing 94.5% ISB as determined by HPLC, with the remaining 5.5% consisting of "closely related isomers" produced during synthesis. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, No. 2:16-cv-00491, 2016 WL 7587325, at *2 (E.D. Tex. Nov. 21, 2016) ("*Report and Recommendation*") (internal quotation marks omitted).

For 26 years following the Food and Drug Administration's ("FDA") approval of ISB, Sigma-Aldrich Corp. ("Sigma") supplied Hirsch and its successors with ISB that was manufactured by Allied Chemical Corp. ("Allied"). Allied's manufacturing process was unknown, but analysis of its ISB indicated the presence of lead, which suggested the use of a lead compound in synthesis. Sigma developed an isolation process to remove the unwanted lead, but the ultimate purity of the ISB it sold was unknown. In 2000, Allied stopped supplying Sigma with

ISB and, while Sigma was looking for a new supplier, Covidien was forced to notify its customers that it was "completely out of" Lymphazurin® until it could find a new supplier for ISB. *Id.* at *2 (internal quotation marks omitted). By 2008, Sigma had a new supplier, Innovassynth, which synthesized ISB using ammonium dichromate, resulting in residual chromium impurities. Sigma reported numerous problems with the purity of Innovassynth's product and eventually developed its own manufacturing process for ISB sometime around 2010.

Apicore was founded in 2003 and began developing an improved process for synthesizing ISB. In 2004, Apicore partnered with Synerx Pharma LLC ("Synerx"), Mylan Inst.'s predecessor, to develop and market a generic version of Lymphazurin®. In 2007, Apicore filed a patent application that ultimately led to the process and '050 patents. Based on the claimed process, Synerx (acquired by Mylan Inst. in 2012) filed an abbreviated new drug application ("ANDA") seeking FDA approval to market a generic Lymphazurin®; the FDA approved the ANDA in 2010. By 2011, ISB sales were a significant portion of Apicore's revenue and in 2012, Covidien withdrew Lymphazurin® from the market for "reasons other than safety or effectiveness." *Id.* at *3 (internal quotation marks omitted). Mylan Inst. became the sole supplier of the 1% ISB drug product until 2016, when Aurobindo entered the market.

Aurobindo sought FDA approval for a generic Lymphazurin®, informing the FDA that it had studied a "number of patents" describing ISB manufacture and selected, *inter alia*, Apicore's '992 patent, and that it "considered the process described [therein] for the initial sample preparation and further, the optimization of the process." *Id.* (internal quotation marks omitted). Aurobindo acknowledged to the FDA that it was looking for a reagent "other than silver oxide." *Id.* (internal quotation marks omitted). It eventually selected manganese diox-

ide, and its process resulted in ISB with a 5–10% impurity which could not be removed by recrystallization. Instead, it used preparatory HPLC to achieve an ISB purity of greater than 99.5%. Mylan sued Aurobindo for infringement and sought a preliminary injunction, which the district court granted.

First, the district court[2] evaluated the likelihood of success on the merits and found that Aurobindo likely infringed the process patents under the doctrine of equivalents. *Id.* at *10–12. The court found that the difference in oxidation strength between silver oxide and manganese dioxide is "irrelevant" under both the "function-way-result" ("FWR") and "insubstantial differences" tests for equivalence, as applied to the "face of the claims," because the claims do not specify a requirement of oxidation strength. *Id.* at *11. Further, the court explained that, even if oxidation strength were relevant, it "finds manganese dioxide to be a mild oxidant equivalent to silver oxide in the context of the [process patents]." *Id.* The court credited Dr. Sessler's (Mylan's expert) testimony in light of record evidence that the silver oxide and manganese dioxide processes produce crude ISB in similar yields. The court explained that if manganese dioxide were a substantially stronger oxidizing agent than silver oxide, a skilled artisan "would expect different results." *Id.* at *12.

The district court found that Aurobindo did not raise a substantial question of validity of the '050 patent based on its arguments that the process patent is invalid: (1) under § 112 because the "by HPLC" limitation renders

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[2] Because the district court adopted the magistrate judge's report and recommendation, *see Order Adopting R&R*, 2017 WL 497593, at *1, we shall refer to both the district court judge's and magistrate judge's findings and conclusions as those of the district court.

the claims indefinite; (2) under § 103 because the claims would have been obvious over various combinations of art; and (3) under § 102 because the claims are anticipated by Sigma's manufacture and sale of ISB.

On the issue of indefiniteness, the district court credited Sessler's testimony and found that "by HPLC" was a common and well-understood way of designating or determining purity, as seen in "numerous sources," including other patents and the scientific literature. *Id.* at *8–9. Thus, the court concluded that Aurobindo had not raised a substantial question of validity of the '050 patent under § 112. *Id.*

The district court also rejected Aurobindo's obviousness argument, finding that Aurobindo did not raise a substantial question regarding motivation to combine the references or a reasonable expectation of success. *See id.* at *22. The court noted that "a purified compound is not always prima facie obvious over the [prior art] mixture" if the process to arrive at the purified compound is itself of patentable weight. *Id.* at *18 (citing *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)) (internal quotation marks omitted). The court concluded that Apicore's process leading to the purified compound claimed in the '050 patent constituted "an invention of patentable weight itself" and thus the purity claims would not necessarily have been prima facie obvious over the prior art mixture of (less pure) ISB and "closely related isomer[]" by-products. *Id.* at *18, *19 (internal quotation marks omitted).

The district court credited Mylan's evidence of secondary considerations—specifically, long-felt but unmet need, commercial success, copying/praise of others, and unexpected results. *Id.* at *20–22. The court pointed to the failure of Allied, Sigma, Innovassynth, and others in the art to "reliably" produce "high-purity" ISB for 30 years. *Id.* at *20. And the court emphasized that Auro-

bindo "admitted to the FDA" that it had copied the '992 patent. *Id.* at *21. Thus, the court concluded that Aurobindo had not raised a substantial question that the '050 patent is invalid as obvious. *Id.*

The district court also concluded that Aurobindo had not raised a substantial question that the '050 patent claims were anticipated under § 102(b) and § 102(g)(2) by Sigma's manufacture and sale of ISB. *See id.* at *13. Aurobindo argued that Sigma had made and sold ISB having a purity of greater than 99.0% six years before the '050 patent priority date. *See id.* Aurobindo supported its position by citing a Sigma Certificate of Analysis, which indicated that a compound named "Patent Violet Blue," with a certain product number and Lot number, possessed a purity that was 100% by HPLC. *Id.* The court rejected Aurobindo's argument, finding that: (1) it is not clear that, at the time of the Certificate, Sigma's use of the term "Patent Violet Blue" referred to ISB because other Sigma documents indicate that "Patent Violet Blue" referred to several blue dye compounds with different structures; and (2) the record established that the Certificate is inaccurate because it "contradicts numerous other Sigma[] documents" that report a different purity for samples from the same Lot. *Id.* at *14. Thus, the court concluded that Aurobindo had not raised a substantial question that the '050 patent is invalid as anticipated. *Id.*

Second, the district court found that Apicore[3] would be irreparably harmed without a preliminary injunction and identified four "hallmark examples" of irreparable harm that are demonstrated by the record: lost sales; lost R&D; price erosion; and that Apicore must now directly compete with an infringer. *Id.* at *23; *Order Adopting R&R*, 2017 WL 497593, at *1.

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[3] The court only analyzed "irreparable harm" as to Apicore, a fact that neither party challenges on appeal.

The district court found a "causal nexus" between Aurobindo's infringement and Apicore's harm in that Aurobindo's product "would not be on the market if [it] had not obtained [FDA] approval for a product that will likely be found to be covered by the patents." *Order Adopting R&R*, 2017 WL 497593, at *1. The court noted that "[w]ithout infringing the '992, '616, and '050 patents, Aurobindo would not be able to make the [ISB] product described in its ANDA" because Aurobindo's ANDA application touted greater than 99.0% purity for ISB. *Report and Recommendation*, 2016 WL 7587325, at *24.

Third, the district court found that the balance of equities weighed in favor of granting the injunction. *Id.* The court emphasized that Apicore "stands to lose its entire [ISB] business, . . . which it relies on to fund ongoing research and development," and that Aurobindo was aware of Apicore's patented process and copied it. *Id.* Thus, the court found that the balance of equities favored Apicore. *Id.* (citing *Windsurfing Int'l Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 (Fed. Cir. 1986) ("One who elects to build a business on a product found [likely] to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected.")).

Finally, the district court found that the public interest factor also favored granting the preliminary injunction. The court observed that Apicore satisfied its end of the patent bargain by disclosing its method for preparing ISB and that it would likely not have done so if it had known that a competitor would use that method to destroy its ISB business before it "could make it to trial." *Id.* The court emphasized that the public interest in obtaining lower-priced pharmaceutical compounds cannot justify "entirely eliminating the exclusionary rights covered by pharmaceutical patents." *Id.* (internal quotation marks omitted).

Aurobindo appeals the district court's grant of a preliminary injunction. We have jurisdiction pursuant to 28 U.S.C. § 1292(a)(1) and (c)(1).

DISCUSSION

The grant or denial of a preliminary injunction is within the sound discretion of a district court, and we will not reverse its judgment absent an abuse of that discretion. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001). Accordingly, we will only overturn a decision granting a preliminary injunction on appeal if "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." *Sanofi–Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1374 (Fed. Cir. 2006) (quoting *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997)). We review the district court's conclusions of law de novo. *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1325 (Fed. Cir. 2004).

"A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008).

On appeal, Aurobindo disputes the court's findings that Aurobindo "more likely than not" infringes the process patents under the doctrine of equivalents, *Report and Recommendation*, 2016 WL 7587325, at *12; Aurobindo did not raise a substantial question as to validity of the '050 patent; and there was irreparable harm to Apicore. We discuss each issue in turn.

I. Process Patents

We first consider whether the district court erred in finding that Mylan is likely to succeed on the merits because Aurobindo "more likely than not" infringes the process patents under the doctrine of equivalents. *Report and Recommendation*, 2016 WL 7587325, at *12. To establish a likelihood of success on the merits, a patentee must show that it will likely prove infringement of the asserted claims and that its infringement claim will likely withstand the alleged infringer's challenges to patent validity and enforceability. *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012) (citing *Amazon.com*, 239 F.3d at 1350). A preliminary injunction should not issue if the accused infringer "raises a substantial question concerning either infringement or validity." *Amazon.com*, 239 F.3d at 1350.

Aurobindo argues that it had raised a substantial question of infringement of the process patents under the doctrine of equivalents because manganese dioxide oxidizes isoleuco acid in a different way than silver oxide in that manganese dioxide is a strong oxidizing agent, whereas silver oxide is a weak oxidizing agent. Additionally, Aurobindo continues, manganese dioxide oxidation requires the use of an acid and the patents specifically report the use of silver oxide as not requiring an acid.

Mylan responds that the district court correctly found a likelihood of success on the merits of infringement under the doctrine of equivalents because the court properly found that manganese dioxide and silver oxide are equivalent in the context of the process patents. Specifically, the court credited Sessler's testimony in light of record evidence that the silver oxide and manganese dioxide processes produce crude ISB in similar yields. The court explained that if manganese dioxide was a substantially stronger oxidizing agent than silver oxide, a skilled artisan "would expect different results." *Report*

and Recommendation, 2016 WL 7587325, at *12. That finding, Mylan argues, was not clearly erroneous.

As set forth below, we conclude that the district court's analysis of equivalence in this case was flawed, no doubt because of the sparse and confusing case law concerning equivalents, particularly the paucity of chemical equivalence case law, and the difficulty of applying the legal concepts to the facts. We will attempt to provide more clarity on these subjects.

This appeal is unusual in a first sense in that it arises from the grant of a preliminary injunction based on the doctrine of equivalents. There are few such reported decisions, *but see, e.g.*, *Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1378 (Fed. Cir. 2005), owing to the fact that equivalents cases are "highly factual inquir[ies] [that] rarely come[] clear on a premature record." *Jeneric/Pentron, Inc. v. Dillon Co., Inc.*, 205 F.3d 1377, 1384 (Fed. Cir. 2000). Moreover, the law on the doctrine of equivalents as applied to chemical materials is not clear, and its misapplication can lead to unsound results. This appears to be such a case.

In *Graver Tank*, the Supreme Court set out two frameworks for evaluating equivalence—the familiar FWR test (viz., whether the accused product performs "substantially the same function in substantially the same way to obtain the same result") and the insubstantial differences test (whether the accused product or process is substantially different from what is patented). *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S. 605, 608, 609 (1950). The Supreme Court's most recent visit with this branch of the law was in *Warner-Jenkinson*, which dealt with whether a process of purification performed at a pH of 5 was equivalent to one performed at a pH of 6–9. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39 (1997). The Court noted that equivalence is not a "prisoner of formula," *id.* at 39,

but also observed that non-mechanical cases may not be well-suited to consideration under the FWR test, *see id.* at 39–40 ("There seems to be substantial agreement that, while the [FWR] test may be suitable for analyzing mechanical devices, it often provides a poor framework for analyzing other products or processes.").

The Supreme Court was surely correct in stating that non-mechanical cases may not be well-suited to consideration under the FWR test. That seems to be particularly true in the chemical arts. Although in *Graver Tank*, the Supreme Court recognized the use of FWR generally in chemical cases, 339 U.S. at 608 ("Today the doctrine [of equivalents] is applied to mechanical or chemical equivalents in compositions or devices."), the Court later acknowledged in *Warner-Jenkinson* that the suitability of the two tests may vary, depending on the circumstances of the case, 520 U.S. at 40 ("Different linguistic frameworks may be more suitable to different cases, depending on their particular facts."). Thus, the Court seemingly blessed two equivalents tests, leaving to the lower courts in future cases the choice of which to apply.

The district court here applied the FWR test in evaluating the equivalence issue.[4] We will therefore review its decision first in that light. In doing so, we conclude that

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[4] We note that the district court recognized that the FWR test "may inform whether insubstantial differences exist between a claim element and an accused element." *Report and Recommendation*, 2016 WL 7587325, at *11. Under that analysis, the district court concluded that "the oxidation strength of manganese dioxide is irrelevant under the insubstantial difference test," dismissing any consideration of oxidation strength on claim construction grounds, as will be discussed further below. *Id.* Thus, the district court did not evaluate whether silver oxide and manganese dioxide are insubstantially different.

the district court's analysis of the process claims under FWR was flawed by being unduly truncated and hence incomplete.

Especially when evaluating an equivalents dispute dealing with chemical compositions having many components, chemical compounds with many substituents (which are usually claimed as separate limitations), and those having a medical or biological use, it is often not clear what the "function" or "way" is for each claim limitation. How a particular component of a composition, or substituent of a compound, functions in a human or animal body, or in what way, may not be known or even knowable (although, as technology evolves, that may change). And precedent requires that, for infringement under the doctrine of equivalents, each limitation must satisfy an equivalence test. *See Warner-Jenkinson*, 520 U.S. at 40.

The "result" of using a claimed compound may be more easily evaluated, as the structure and uses of one compound may be directly compared with those of another. But, as indicated above, that is not how infringement under FWR is determined. It must be determined on a limitation-by-limitation basis. *See id.* Similarly, in the case of a chemical process claim, as in this case, the "result" of a process producing a chemical compound may be clear[5]—why else would a claim for infringement of a process claim be brought if the claimed result is not obtained? But the "function" and "way" of a particular

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[5] In this case, the parties did not dispute the "result" prong before the magistrate judge, but did do so before the district court judge, who did not address those arguments. Thus, the court never made a finding on the "result" prong. However, we need not decide whether that constituted reversible error because we modify the preliminary injunction for other reasons set forth herein below.

limitation of a chemical process claim may remain vague and often overlap. In some cases, "way" and "function" may be synonymous.

Aurobindo argued before the district court that the "function" prong of the FWR test was not met because of the difference in oxidation strength between silver oxide and manganese dioxide. But the court did not seem to address that argument, which in actuality related to the "way" component of the FWR test. The court stated that "[c]onverting the isoleuco acid to isosulfan blue acid *is the function* of the silver oxide," and then dismissed Aurobindo's oxidation strength argument as "irrelevant" to the FWR and "insubstantial difference" tests. *Report and Recommendation*, 2016 WL 7587325, at *11 (emphasis added). Nevertheless, the court made a finding that silver oxide and manganese dioxide are "equivalent" in the context of the process patents, without considering the "way" prong of the FWR test. *Id.* In fact, the court appeared to consider the relative oxidation strengths of silver oxide and manganese dioxide as a consideration for claim construction, rather than its equivalents analysis. *Id.* at *10–12 (stating that the relative oxidation strengths are "*irrelevant*" for both the FWR and insubstantial differences tests and that Aurobindo had not argued for a "narrow[er]" claim construction that would read an oxidation strength limitation into the claims, but noting that a "more fully-developed factual record and *claim construction proceeding* could change things" (emphases added)).

Thus, either the district court did not address the "way" prong of the FWR analysis—having considered the relative oxidation strengths to be an issue for claim construction, and rejecting Aurobindo's arguments about oxidation strength because it had not argued for a narrow claim construction—or it performed a "way" analysis without considering critical factors under that prong, namely, the relative oxidation strengths of silver oxide

and manganese dioxide, as well as the use of an acid in the accused process. Either characterization constitutes error in the court's equivalents analysis.

The district court correctly evaluated the "function" aspect of the FWR test—deciding, in effect, that the function of the silver oxide was to oxidize the precursor isoleuco compound to ISB acid.[6] But that is not considering the "way" the oxidation works. Manganese dioxide and silver oxide may have the same *function*, but the question is whether they operate in the same *way*. Critical facts that might be considered in an equivalents analysis include the relative oxidation strengths of the two oxidizing agents, as argued by Aurobindo, and the fact that manganese dioxide requires the use of an acid for oxidation, but silver dioxide does not, and results in a different yield. All of this in fact may at trial indicate a different "way." Thus, there is room for sufficient doubt as to whether silver oxide and manganese dioxide oxidize isoleuco acid in the same way so as to satisfy the "way" prong of the FWR test.

Accordingly, the district court erred in its equivalents analysis under FWR and we reverse its determination. When the case goes back to the district court for a full trial on the merits, the court may wish to consider whether the substantiality of the differences test may be more applicable in this case. Even if evaluating the "function"

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[6] We note that the court seemed to make a finding as to the "function" prong, without stating it as such. It acknowledged that Aurobindo only disputed the "function" of the oxidizing agents, but then stated that "[c]onverting the isoleuco acid to isosulfan blue acid *is the function* of the silver oxide," while rejecting Aurobindo's arguments on claim construction grounds. *Id.* at *11 (emphasis added). We will treat that part of the court's analysis as its finding under the "function" prong of the FWR test.

and "way" prongs is feasible, the FWR test may be less appropriate for evaluating equivalence in chemical compounds if it cannot capture substantial differences between a claimed and accused compound.

For example, consider the well-known compounds aspirin and ibuprofen, which chemists would not usually consider to be structural equivalents under the insubstantial differences test. Chemical compounds are characterized by their structures, and these two compounds differ substantially in structure (see appendix). However, the two compounds would seem to be substantial equivalents under the FWR test. They each provide analgesia and anti-inflammatory activity ("function") by inhibiting prostaglandin synthesis ("way") in order to alleviate pain, reduce fevers, and lessen inflammation ("result"). *See, e.g.*, *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1546 (Fed. Cir. 1995) (Lourie, J., dissenting). Thus, a compound may appear to be equivalent under the FWR test, but not under the substantiality of the differences test. Hence, the substantial differences test may be more suitable than FWR for determining equivalence in the chemical arts. *Warner-Jenkinson*, 520 U.S. at 40 ("Different linguistic frameworks may be more suitable to different cases, depending on their particular facts.").

In this case, the district court conducted an incomplete FWR analysis while essentially bypassing the substantial differences test, in a situation where the latter test might seemingly be more appropriate. The claims in the process patents recite a method for preparing a specifically named compound by combining another specifically depicted compound with a third specific compound, *viz.*, silver oxide. Each of these compounds is expressly named, and an infringement analysis must not take lightly the specific recitation of these materials. The district court found that the accused process using manganese dioxide was equivalent to the claimed process using silver oxide. But the court failed to consider wheth-

er the key reagent in the process, manganese dioxide, was *substantially different from* the claimed reagent, silver oxide, and hence whether the substitution for, and omission of, silver oxide left the accused infringer outside of the bounds of the claims.

Manganese dioxide and silver oxide are substantially different in many respects. For example, manganese and silver are in different groups of the Periodic Table. In oxide form, manganese has an oxidation state of +4, while silver is +1. Those differences may well be relevant to equivalence at trial. Thus, the choice of test under the doctrine of equivalents may matter in this case.

When the case returns to the district court for a full trial on the merits, the court should, in addition to providing further analysis regarding fulfillment of the FWR test, if it determines that it should still utilize that test, also consider whether an evaluation of equivalence under the substantial differences test may be better suited to the particular facts of this case.

In sum, we conclude that the court's equivalents analysis was deficient in its FWR analysis. Because, on the record, there remains a substantial question concerning infringement, we conclude that the court's grant of a preliminary injunction based on the process patents constituted an abuse of discretion. Thus, we modify[7] the court's grant of the preliminary injunction to premise it

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[7] Ordinarily a failure by the district court to properly apply the doctrine of equivalents would warrant a remand. However, because the injunction will stand under the '050 patent, as will be discussed *infra*, we see no need to expend judicial resources and litigation expenses on a remand. Thus, we will modify the district court's decision by affirming the grant of a preliminary injunction premised only on the '050 patent.

only on its evaluation of the '050 patent, as will be discussed *infra*.

II. '050 Patent

We next consider whether the district court erred in finding that Aurobindo did not raise a substantial question as to validity of the '050 patent. *Id.* at *14, *23. Aurobindo does not appeal the court's finding that it "more likely than not" infringes the '050 patent. *Id.* at *12. Thus, the preliminary injunction premised on the '050 patent will stand unless Aurobindo raised a substantial question concerning the validity of the patent, or unless the court erroneously found irreparable harm. We find that the court did not err in either respect.

Aurobindo argues that the claims of the '050 patent are anticipated by Sigma's ISB product because a Sigma Certificate of Analysis shows that Sigma made and sold ISB with a purity of 100% six years before the relevant date of the '050 patent. Furthermore, Aurobindo argues that the '050 patent would have been obvious over Lymphazurin® itself because the prior art taught the use of HPLC and other conventional purification techniques for purifying ISB. Finally, Aurobindo argues that the '050 patent is invalid because the limitation "having a purity of at least 99.0% by HPLC" is indefinite. Aurobindo contends that different HPLC parameters will produce different results in a purity analysis and thus, because the claims do not specify HPLC parameters, they are indefinite.

Mylan responds that the district court's findings regarding a lack of a substantial question of validity due to anticipation, obviousness, and indefiniteness were not clearly erroneous.

We agree with Mylan. Aurobindo points to no legal error in the district court's analysis of the record evidence; rather, it argues only that the court erred in "misreading

the factual content of the prior art." Appellant's Br. 43. However, what the prior art teaches is a question of fact that we review with deference, especially at the preliminary injunction stage. *Amazon.com*, 239 F.3d at 1358. We do not "reweigh evidence on appeal." *In re NTP, Inc.*, 654 F.3d 1279, 1292 (Fed. Cir. 2011).

The district court rejected Aurobindo's argument that the '050 patent claims are anticipated by Sigma's manufacture and sale of ISB because it found that the Sigma Certificate of Analysis related to a compound named "Patent Violet Blue" and it was not clear that, at the time of the issuance of the Certificate, Sigma used that term to refer to ISB. Additionally, the Certificate contradicts other Sigma documents that report different purity levels for samples from the same Lot. *Report and Recommendation*, 2016 WL 7587325, at *14. We discern no clear error in those findings.

The district court also rejected Aurobindo's obviousness argument, finding that Aurobindo did not raise a substantial question regarding motivation to combine the references or a reasonable expectation of success. *See id.* at *22. The court found that Apicore's *process* leading to the claimed ISB product with a purity of greater than 99.0% constituted "an invention of patentable weight itself" and thus that the '050 patent claims would not necessarily have been prima facie obvious over the prior art mixture of (less pure) ISB and "closely related isomer[]" by-products. *Id.* at *18, *19 (internal quotation marks omitted).

Finally, the district court rejected Aurobindo's argument that the '050 patent claims are invalid as indefinite. The court found that the phrase "by HPLC" was a "common and well understood way of designating purity in publications and patents that are relied upon by the scientific and technical community." *Id.* at *8 (quoting Sessler's testimony). The court found that "numerous

sources" support that determination, including patents filed before the relevant date of the '050 patent.

We see no error in the district court's analysis. We have previously acknowledged that "a purified compound is not always prima facie obvious over the [prior art] mixture" if the process to arrive at the purified compound is itself of patentable weight. *Aventis*, 499 F.3d at 1301. Moreover, if the prior art teaches a mixture containing a compound but does not *enable* its purification, then the purified form of the compound may not have been obvious over the prior art mixture. *See, e.g.*, *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1335–36 (Fed. Cir. 2015) (concluding that a purified compound would have been obvious over the prior art mixture where, *inter alia*, "the whole spectrum of prior art available before the invention was made would have *enabled one of skill in the art* to make and use the claimed substantially pure . . . compound" (emphasis added)). The court expressly relied on the *Aventis* proposition in making its determination. *Report and Recommendation*, 2016 WL 7587325, at *17–18 (quoting *Aventis*, 499 F.3d at 1301). We see no error in its analysis. It is clear from the record here that, although ISB was known in the prior art, the path to arrive at ISB with a purity of greater than 99.0% was not known before the relevant date of the '050 patent.

Furthermore, the district court credited Mylan's evidence of secondary considerations—specifically, long-felt but unmet need, commercial success, copying/praise of others, and unexpected results. *Id.* at *20–22. The court relied on record evidence showing the failure of Allied, Sigma, Innovassynth, and others in the art to "reliably" produce "high-purity" ISB for 30 years, *id.* at *20, and that Aurobindo "admitted to the FDA" that it had copied the '992 patent, *id.* at *21. There is no clear error in the court's findings. In fact, the record demonstrates that, prior to the '050 patent's relevant date, a reliable source of high-purity ISB was so scarce that, at one point,

Covidien was forced to notify its customers that it was "completely out of" Lymphazurin® until it could find a new supplier for ISB. *Id.* at *2 (internal quotation marks omitted).

Finally, there is no error in the court's determination that the '050 patent is likely not invalid as indefinite. The court's finding was supported by substantial record evidence, including the scientific literature and other patents reporting purity using the same "by HPLC" designation without providing specific HPLC parameters. *Id.* at *8. The court found that even Dr. Brown's testimony (Aurobindo's expert) admitted that "purity by HPLC" is typically used in FDA submissions for describing purity levels. *Id.* at *9. Thus, the court determined that a skilled artisan "would readily understand" the phrase and would be able to "elucidate HPLC conditions" for determining ISB purity. *Id.* We see no error in that finding.

Thus, we see no error in the court's legal analysis or its factual findings pertaining to validity of the '050 patent, particularly at the preliminary injunction stage of the litigation.

III. Irreparable Harm

Finally, we consider whether the district court erred in finding a likelihood that Apicore will sustain "substantial and immediate irreparable injury" without preliminary relief. *Id.* at *22 (citing *Apple, Inc. v. Samsung Elects. Co.*, 678 F.3d 1314, 1325 (Fed. Cir. 2012)) (internal quotation marks omitted).

Aurobindo argues that the district court erred in finding a causal nexus between Apicore's alleged harm and the patented features of the process and '050 patents. Aurobindo contends that the patented features are the use of silver oxide to oxidize isoleuco acid, and that the ISB employed in the finished drug product is at least 99.0% pure by HPLC. However, Aurobindo argues, there

is no evidence that the consumer demand for Mylan's product arises from the fact that the ISB it contained was synthesized using silver oxide or that the ISB is at least 99.0% pure; in fact, argues Aurobindo, that information is not available anywhere on Mylan's marketing materials for its ISB drug product. Rather, Aurobindo continues, the record shows that there was no consumer demand for the patented product because Lymphazurin® was commercially successful until Mylan Inst.'s product drove it out of the market due to *pricing*—not due to the difference in the manufacturing process or purity of the ISB it contains.

Mylan responds that Aurobindo's causal nexus argument is flawed because it improperly focuses on a subset of the relevant customers (physicians) and ignores all others (active pharmaceutical ingredient ("API") suppliers, pharma companies, hospitals, the FDA, etc.). Mylan maintains that Apicore's harm is directly caused by Aurobindo's infringement because ample evidence shows Sigma's difficulty in finding an acceptable ISB supplier and that, by admittedly copying Apicore's patented process, Aurobindo gained a competitive advantage.

We agree with Mylan that the district court's determinations were not clearly erroneous. On the record evidence, the court found that: (1) due to Aurobindo's infringement, Apicore has, and will continue to, suffer from lost sales, lost research and development, price erosion, and having to directly compete with an infringer, *id.* at *23; (2) there was a causal nexus between Aurobindo's infringement and Apicore's harm because Aurobindo's product "would not be on the market if [it] had not obtained [FDA] approval for a product that will likely be found to be covered by the patents," *Order Adopting R&R*, 2017 WL 497593, at *1; and (3) "[w]ithout infringing the [process and purity] patents, Aurobindo would not be able to make the [ISB] product described in its ANDA," *Report and Recommendation*, 2016 WL 7587325, at *24.

Those findings do not constitute clear error. Aurobindo argues that the court could not rely on the FDA's approval of Aurobindo's ANDA application to automatically find a causal nexus between Apicore's harm and Aurobindo's infringement. But that is not what the court found or how the court used that evidence. The record evidence shows Aurobindo's admitted copying of Apicore's '992 patent, *id.* at *4, Aurobindo's ANDA promising an ISB purity of greater than 99.0%, *id.* at *24, and the failure of all others in the art to obtain an ISB purity of greater than 94.5% until the invention of the '050 patent, *id.* at *20. Thus, the district court reasonably found that, "[w]ithout infringing the [process and '050] patents, Aurobindo would not be able to make the [ISB] product described in its ANDA." *Id.* at *24. In making that determination, the court did not rely on regulatory approval to automatically confer a causal nexus, as Aurobindo argues. Rather, it made a reasoned factual determination, supported by substantial record evidence. We see no legal error in the court's analysis and no clear error in its factual findings.

Aurobindo does not challenge the district court's findings that the balance of equity and public interest factors weigh in favor of granting the preliminary injunction. Thus, because we find no error in the court's determination that Aurobindo has not raised a substantial question of validity of the '050 patent and that Apicore will be irreparably harmed without preliminary relief, we affirm the district court's grant of the preliminary injunction premised on the '050 patent.

CONCLUSION

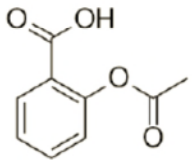
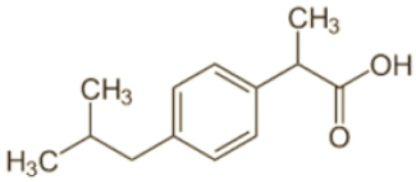
We have considered the parties' remaining arguments, but find them to be unpersuasive. For the reasons set forth above, we modify the court's grant of a preliminary injunction by premising it only on the '050 patent.

AFFIRMED

COSTS

No costs.

APPENDIX

Aspirin*:	Ibuprofen**:
	

* acetylsalicylic acid

** (*RS*)-2-(4-(2-methylpropyl)phenyl)propionic acid