United States Court of Appeals for the Federal Circuit

ADAPT PHARMA OPERATIONS LIMITED, ADAPT PHARMA, INC., ADAPT PHARMA LIMITED, OPIANT PHARMACEUTICALS, INC.,
Plaintiffs-Appellants

v.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES, LTD.,
Defendants-Appellees

2020-2106

Appeal from the United States District Court for the District of New Jersey in Nos. 2:16-cv-07721-BRM-JAD, 2:17-cv-00864-JLL-JAD, 2:17-cv-02877-JLL-JAD, 2:17-cv-05100-JLL-JAD, 2:18-cv-09880-JLL-JAD, Judge Brian R. Martinotti.

Decided: February 10, 2022

CATHERINE EMILY STETSON, Hogan Lovells US LLP, Washington, DC, argued for all plaintiffs-appellants. Plaintiffs-appellants Adapt Pharma Operations Limited, Adapt Pharma, Inc., Adapt Pharma Limited also represented by JESSAMYN SHELI BERNIKER, DAVID M. KRINSKY, JESSICA PALMER RYEN, Williams & Connolly LLP, Washington, DC.

JESSICA TYRUS MACKAY, Green, Griffith & Borg-Breen LLP, Chicago, IL, for plaintiff-appellant Opiant Pharmaceuticals, Inc.

JOHN CHRISTOPHER ROZENDAAL, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC, argued for defendants-appellees. Also represented by PAUL ASHLEY AINSWORTH, MICHAEL E. JOFFRE, ADAM LAROCK, WILLIAM MILLIKEN, CHANDRIKA VIRA; LIZA M. WALSH, Walsh Pizzi O'Reilly Falanga LLP, Newark, NJ.

Before NEWMAN, PROST, and STOLL, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* STOLL.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

STOLL, *Circuit Judge*.

Adapt Pharma Operations Limited, Adapt Pharma, Inc., Adapt Pharma Limited, and Opiant Pharmaceuticals, Inc. (collectively, "Adapt") appeal the United States District Court for the District of New Jersey's final judgment of invalidity. After a two-week bench trial, the district court determined that the asserted claims of U.S. Patent Nos. 9,468,747; 9,561,177; 9,629,965; and 9,775,838 (collectively, the "patents-in-suit") would have been obvious in view of the prior art. For the reasons below, we conclude that the district court did not err in its obviousness determination and therefore affirm.

BACKGROUND

I

The patents-in-suit claim methods of treating opioid overdose by intranasal administration of a naloxone formulation, as well as devices for intranasal administration. Naloxone—the active ingredient in Adapt's NARCAN®

Nasal Spray—is an opioid receptor antagonist that blocks opioids from reaching the opioid receptors, thus helping reverse the effects of opioid overdose. '747 patent col. 2 ll. 13–15.[1]

The use of naloxone to treat opioid overdose was not a new concept at the time of the invention. Before the priority date of the patents-in-suit, numerous naloxone products had been used to treat opioid overdose. For example, the specification explains that naloxone "approved for use by injection" was an option for treating opioid overdose. *Id.* It was also known in the prior art to administer naloxone intranasally. For example, before the priority date, naloxone was administered intranasally by "combin[ing] an FDA-approved naloxone injection product with a marketed[] medical device called the Mucosal Atomization Device." *Id.* at col. 6 ll. 46–51. This device, which the parties and the district court refer to as the MAD Kit, allows a liquid formulation to be sprayed into the nostrils. The specification also describes a number of prior art studies that administered 2 mg of naloxone intranasally to overdose victims, *id.* at col. 3 l. 1–col. 4 l. 26, col. 5 ll. 29–54 (citations omitted), and another that administered 8 mg and 16 mg of naloxone intranasally, *id.* at col. 5 l. 55–col. 6 l. 3 (citing PCT Pub. No. WO 2012/156317).

Administering naloxone by injection or using the MAD Kit was not without disadvantages. For example, the specification explains that only trained medical personnel can administer naloxone by injection (either intramuscularly, which is an injection in the muscle, or intravenously, which is an injection in the vein), *id.* at col. 6 ll. 14–35, preventing many first responders from administering naloxone to overdose victims. And while the MAD Kit provided first

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[1] Each of the patents-in-suit are in the same family and have overlapping specifications, so we generally cite only the '747 patent's specification.

responders with a mechanism to quickly administer naloxone intranasally, it too had disadvantages in that it required assembly prior to use and delivered too much fluid into the nose.

On April 12, 2012, amidst the growing opioid addiction crisis, the U.S. Food & Drug Administration (FDA) held a public meeting to "promote and encourage the industry to develop an intranasal naloxone product that could be FDA-approved." J.A. 3859–60 (Trial Tr. 336:16–337:3). At this meeting, the FDA explained that any intranasal naloxone formulation should provide exposure at least comparable to already-approved injectable naloxone products. That is, the intranasal formulation should deliver the same amount of drug to the bloodstream as the injectable formulations. Shortly thereafter, on May 24, 2012, Lightlake Therapeutics, Inc.—Opiant's predecessor—met with the FDA to discuss a potential investigational new drug application. Although Lightlake expressed its view that there was "little if any commercial incentive" to develop an intranasal product, J.A. 3824 (Trial Tr. 301:3–17), it nevertheless sought input from the FDA on its plans to develop a 2 mg intranasal naloxone formulation, relying on an approved 2 mg intramuscular naloxone formulation as a reference formulation. In response, the FDA explained that numerous studies indicated that a 2 mg intranasal dose would have poor bioavailability compared to a 2 mg intramuscular dose and therefore recommended that Lightlake increase the dose of its proposed product to achieve bioavailability similar to the intramuscular product. Lightlake did just that, ultimately submitting New Drug Application (NDA) No. 208411 for a 4 mg intranasal naloxone product, approved under the name NARCAN®.[2]

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[2] Adapt is the current holder of the NDA for NARCAN® Nasal Spray.

On March 16, 2015, Adapt filed U.S. Patent Application No. 14/659,472, from which each of the patents-in-suit claim priority. All of the patents-in-suit are listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book, as covering NARCAN®. At trial, the district court treated dependent claim 9 of the '747 patent as representative, which includes claims 1 and 2 in its dependency. Because the issues on appeal relate to the formulation limitations of the asserted claims, which are recited in claims 1 and 2, we reproduce only those claims below:

> 1. A method of treatment of opioid overdose or a symptom thereof, comprising nasally administering to a patient in need thereof a dose of naloxone hydrochloride using a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:
>
> about 4 mg naloxone hydrochloride or a hydrate thereof;
>
> between about 0.2 mg and about 1.2 mg of an isotonicity agent;
>
> between about 0.005 mg and about 0.015 mg of a compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer;
>
> between about 0.1 mg and about 0.5 mg of a stabilizing agent; and
>
> an amount of an acid sufficient to achieve a pH of 3.5-5.5.

2. The method as recited in claim 1 wherein:

the isotonicity agent is NaCl;

the preservative is benzalkonium chloride;

the stabilizing agent is disodium edetate; and

the acid is hydrochloric acid.

'747 patent col. 53 ll. 8–29.

II

Teva Pharmaceuticals USA, Inc. and Teva Pharmaceuticals Industries, Ltd. (collectively, "Teva") asserted two different combinations of prior art at trial: (1) Davies[3] in view of Kerr 2009[4]/the Kerr Formulation and Bahal[5] (the "Davies combination"); and (2) Strang[6] in view of Kulkarni[7] and Djupesland[8] (the "Strang combination"). We discuss each combination and reference in turn.

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[3] PCT Pub. No. WO 2000/62757.

[4] Debra Kerr et al., *Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose*, 104 Addiction 2067–74 (2009).

[5] U.S. Patent No. 5,866,154.

[6] PCT Pub. No. WO 2012/15317.

[7] Vitthal Kulkarni & Charles Shaw, *Formulation and characterization of nasal sprays: An examination of nasal spray formulation parameters and excipients and their influence on key* in vitro *tests*, Inhalation 10–15 (June 2012).

[8] Per Gisle Djupesland, *Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review*, 3 Drug Delivery & Translational Rsch. 42–62 (2013).

A

The first combination involves Davies, Kerr 2009/the Kerr Formulation, and Bahal. Davies relates to spray applicators for administering naloxone and formulations of naloxone for nasal administration. Davies, Abstract. Specifically, Davies "provide[s] systems of administering an opioid antagonist," such as naloxone, "which can be carried out by an unskilled person, rapidly and with a good chance of successfully reviving a patient suffering from opioid over-dosage." *Id.* at 1. Davies provides a detailed description and drawings of a spray applicator that can be used for intranasal administration. *See id.* at 4–5 & Figs. 1–2. Davies teaches that naloxone, the "preferred opioid antagonist," is preferably administered "as a sprayable liquid composition." *Id.* at 2. Davies also teaches that naloxone is "freely soluble in water . . . when in the form of a salt, such as a hydrochloride," and so it therefore may be dissolved in dilute saline solutions such as a solution containing about 0.9% w/v sodium chloride. *Id.* Davies explains that the formulation should be slightly acidic (e.g., pH 6.5), to maintain the naloxone in its salt form. *Id.* at 2, 4. Additionally, Davies teaches that a suitable dose of naloxone for nasal administration ranges from 0.2 to 5 mg, with the volume for administration ranging from 20 to 100 µL. *Id.* at 3. One exemplary naloxone formulation in Davies includes benzalkonium chloride (BZK) as a preservative in an amount of 0.025% w/v. *Id.* Example 1.

Kerr 2009 recognized the benefits of administering naloxone intranasally, noting that intranasal administration is one way to reduce the risk of accidental and unintended needlesticks often associated with injections. Kerr 2009 at 2067–68, 2072. Kerr conducted a study aimed at "determin[ing] the effectiveness and safety of concentrated (2 mg/m[L]) i.n. [intranasal] naloxone compared to i.m. [intramuscular] naloxone for treatment of suspected opiate overdose." *Id.* at 2068. Although the formulation Kerr used in their study (the "Kerr Formulation") was not

disclosed in the reference itself, the evidence and testimony at trial established that the formulation Kerr used was purchased from a third party, ORION Laboratories Pty. Ltd., and is therefore prior art to the patents-in-suit. This is not disputed on appeal. This formulation comprised 0.2% naloxone hydrochloride (HCl) (i.e., 2 mg/mL naloxone HCl), sodium chloride, 0.01% BZK as a preservative, water, and hydrochloric acid to adjust the pH of the solution. J.A. 11467.

Bahal relates to "[p]hysically and chemically stable pharmaceutical compositions useful for administering naloxone by injection." Bahal, Abstract. Bahal describes the "[i]nstability of naloxone," specifically noting that autoclaving naloxone formulations—a process that can be used to sterilize drug products—results in significant naloxone degradation. *Id.* at col. 1 ll. 44–47. After conducting a number of studies, Bahal concluded that the "addition of a chelating agent, such as sodium edetate" (EDTA) "prevents naloxone degradation, even in the presence of oxygen and after autoclaving." *Id.* at col. 1 ll. 53–56.

B

The second combination involves Strang, Kulkarni, and Djupesland. Strang discloses various intranasal naloxone formulations for treating opioid overdose. Strang, Abstract. In particular, Strang discloses intranasal formulations having between 0.5 and 20 mg naloxone HCl, *id.* at p. 5 ll. 16–17, identifying 4 mg as a "preferred" starting dose, *id.* at p. 29 ll. 17–22. Based on measured AUCs[9] for both intravenously and intranasally administered naloxone, Strang "estimated that the range of dose-proportionality to 1 mg IV [intravenous] is in the range of 3 mg to

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[9] AUC (area under the curve) is a measure of bioavailability, that is, the amount of the active ingredient that is absorbed into blood circulation. *Id.* at p. 22 ll. 8–11.

4 mg for IN [intranasal] naloxone." *Id.* Example 2. In other words, Strang determined that the bioavailability for a 1 mg dose of naloxone administered intravenously is about equal to that of a 3 or 4 mg dose of naloxone administered intranasally. Strang further teaches that its naloxone formulations are preferably aqueous saline solutions—that is, solutions comprising about 1.0% sodium chloride in water—and have a pH "most preferably" less than 5.5. *Id.* at p. 9 ll. 22–30. Strang also explains that because naloxone must be present in the bloodstream in an amount sufficient to counter the effect of the opioids, "an effective amount of naloxone has to be provided in one application step," with additional application steps as needed depending on the severity of the overdose. *Id.* at p. 24 ll. 5–10. Additionally, to avoid loss of the drug due to swallowing or leaking from the nostrils, Strang recommends administering intranasal naloxone in small volumes, *id.* at p. 23 ll. 10–13, with 100 µL being "[p]articularly preferred," *id.* at p. 9 ll. 2–3.

Kulkarni is a review article that examines nasal spray formulations and the impact various excipients have on drug performance. Kulkarni provides a table of "key" excipients used in nasal spray formulations, identifying the function and the FDA's concentration limits for each excipient. Kulkarni at 12, Tbl. 2. This list was compiled from the FDA's Inactive Ingredient Guide (IIG) for nasal spray products, which contains "only a limited number of excipients." *Id.* at 12. Kulkarni's table lists (1) BZK, a preservative, in concentrations up to 0.119% w/w; (2) EDTA, a chelating agent, in concentrations up to 0.5% w/w; and (3) sodium chloride, a tonicity agent, in concentrations up to 1.9% w/w. Kulkarni also explains that the "optimal range for pH" of intranasal formulations is between 4.5 and 6.5. *Id.* at 11.

Djupesland is a review article that discusses delivery devices for intranasal administration of drug products. Djupesland explains that, for drugs like naloxone that are

"intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred." Djupesland at 48. Djupesland refers specifically to the Aptar UnitDose device—an FDA-approved medical device that delivers 100 µL of a drug intranasally, J.A. 3858 (Trial Tr. 335:17–21), 11664—as one such spray device for intranasal administration. Djupesland at 48 (citing www.aptar.com).

III

Teva submitted to the FDA Abbreviated New Drug Application (ANDA) No. 209522 seeking approval to manufacture and sell a generic version of NARCAN®. Teva's ANDA filing included a Paragraph IV certification asserting that the patents-in-suit are invalid, unenforceable, and/or not infringed. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). On October 21, 2016, Adapt sued Teva for infringement under 35 U.S.C. § 271(e)(2) based on Teva's ANDA submission. Before trial, Teva stipulated to infringement, and the parties agreed to try validity of a subset of claims, namely: claims 7 and 9 of the '747 patent; claim 4 of the '177 patent; claims 21, 24, and 25 of the '965 patent; and claims 2, 24, 33, and 38 of the '838 patent (the "asserted claims").

The district court held a two-week bench trial on validity. After considering the evidence of record—including testimony from thirteen fact and expert witnesses—the district court issued a nearly 100-page, comprehensive opinion setting forth its findings of fact and conclusions of law under Federal Rule of Civil Procedure 52(a), as well as making specific credibility determinations as to each of the witnesses that testified. *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, Case No. 2:16-cv-7721 (BRM) (JAD), 2020 WL 3428078 (D.N.J. June 22, 2020) (*Judgment Op.*). The district court ultimately determined that Teva had proven by clear and convincing evidence that the

asserted claims would have been obvious in view of the prior art and entered a final judgment of invalidity. *Id.* at *47.

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

DISCUSSION

Following a bench trial, we review the district court's legal determinations de novo and its factual findings for clear error. *See Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017). "A factual finding is only clearly erroneous if . . . we are left with the definite and firm conviction that a mistake has been made." *Id.* "Obviousness is a question of law based on underlying findings of fact." *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019) (quoting *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009)). What the prior art teaches (including whether it teaches away from the claimed invention), whether a skilled artisan would have been motivated to combine the prior art references, and the existence of and weight assigned to any objective indicia of nonobviousness are underlying factual questions we review for clear error. *Merck*, 874 F.3d at 728; *see also AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1335 (Fed. Cir. 2021).

Adapt challenges the district court's determination that the asserted claims would have been obvious over either combination of prior art. Specifically, Adapt challenges several of the district court's factual findings underlying its obviousness determination as clearly erroneous, namely: (1) its finding that a skilled artisan would have been motivated to combine the prior art references to arrive at the claimed invention; (2) its finding that the prior art, as a whole, does not teach away from the claimed invention; and (3) its findings related to Adapt's proffered objective indicia of nonobviousness. We address each issue in turn.

I

We begin with the district court's motivation-to-combine analysis. Adapt's principal argument on appeal is that the district court failed to articulate a reason why a skilled artisan would have been motivated to combine the prior art references to arrive at the claimed invention. We disagree. The district court found that a skilled artisan would have been motivated to: (1) formulate an intranasal naloxone product that would improve upon the MAD Kit; (2) select the claimed excipients—sodium chloride, BZK, EDTA, and hydrochloric acid for adjusting the pH—and the Aptar UnitDose device for intranasal delivery; (3) select a 4 mg dose of naloxone; and, accordingly, (4) combine the prior art references themselves. These findings—supported by ample evidence in the record—provide a detailed explanation as to why a skilled artisan would have been motivated to combine the prior art references to arrive at the claimed invention.

A determination of obviousness "requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." *OSI Pharms.*, 939 F.3d at 1382 (quoting *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018)). This requires "identify[ing] a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). This "motivation to combine may be found explicitly or implicitly in market forces; design incentives; the 'interrelated teachings of multiple patents'; 'any need or problem known in the field of endeavor at the time of invention and addressed by the patent'; and the background knowledge, creativity, and common sense of the person of ordinary skill." *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) (quoting *Perfect Web*

Techs., Inc. v. InfoUSA, Inc., 587 F.3d 1324, 1328–29 (Fed. Cir. 2009)); *accord KSR*, 550 U.S. at 418–21.

First, the district court found that a skilled artisan would have been "motivat[ed] to improve on the MAD Kit because its shortcomings were well-known." *Judgment Op.*, 2020 WL 3428078, at *42. As the district court explained, the FDA in 2012 discussed its "interest in improving the MAD Kit," *id.* at *8 (citing J.A. 3859 (Trial Tr. 336:11–15)), and encouraged the industry to "develop an intranasal naloxone product that could be FDA approved," *id.* (quoting J.A. 3859 (Trial Tr. 336:23–25)). Thus, several years before the priority date of the patents-in-suit, the FDA explicitly provided a motivation to formulate an intranasal naloxone product by identifying a "need or problem known in the [industry] . . . at the time of the invention," *Plantronics*, 724 F.3d at 1354—the known drawbacks of the MAD Kit and the need for an intranasal naloxone product. A skilled artisan, therefore, would have been motivated to develop an intranasal naloxone product.

The prior art references themselves support this conclusion by recognizing the drawbacks of administering naloxone by injection and identifying intranasal naloxone as a solution. For example, crediting the testimony of Teva's expert Dr. Hugh Smyth—whom the district court found to be "highly credible and convincing," *Judgment Op.*, 2020 WL 3428078, at *8—the district court found that Davies "discusses the difficulties associated with medically untrained individuals treating opioid overdoses with injections and discusses how these difficulties could be alleviated with the use of intranasal naloxone." *Id.* at *20 (citing J.A. 3922 (Trial Tr. 399:17–23)). The district court likewise credited Dr. Smyth's testimony that Strang "identified various risks associated with injectable naloxone" and that it "identified intranasal naloxone as a solution to these issues." *Id.* at *19 (first citing J.A. 3890 (Trial Tr. 367:6–15); and then citing Strang at p. 2). Thus, we see no error in the district court's finding that a skilled artisan would have

been motivated to improve upon the MAD Kit and develop an intranasal naloxone formulation for treating opioid overdose.

Second, the district court found that a skilled artisan would have been motivated to use sodium chloride, hydrochloric acid, BZK, and EDTA in an intranasal naloxone formulation. As Dr. Smyth explained, the injectable formulation that was administered using the MAD device was not optimized for intranasal administration. *Id.* at *28 (citing J.A. 3852–53 (Trial Tr. 329:22–330:6)). The district court, therefore, found that a skilled artisan would "have been motivated to optimize th[e] formulation for nasal delivery." *Id.* Relying on testimony of both parties' experts, the district court found that a skilled artisan would have been specifically motivated to use each of the claimed excipients in a nasal formulation. These findings are well-supported by the record.

For instance, the district court found that a skilled artisan would have known that "intranasal formulations generally have certain characteristics to make them acceptable and tolerable in the nose, things like the tonicity and pH." *Id.* (quoting J.A. 3868 (Trial Tr. 345:16–18)); *see also Plantronics*, 724 F.3d at 1354 (explaining that the "background knowledge" of a skilled artisan can provide the requisite motivation to combine). The district court also found that a tonicity agent is often used with intranasal products to avoid nasal irritation and that a skilled artisan would have used the claimed excipient sodium chloride in an intranasal naloxone formulation because it was a well-known tonicity agent. *Judgment Op.*, 2020 WL 3428078, at *28 (first citing J.A. 3868 (Trial Tr. 345:19–346:23); and then citing J.A. 4554 (Trial Tr. 1031:10–15)). Ample evidence before the district court supports this fact finding.

Sodium chloride, for example, was listed in the FDA's Inactive Ingredient Guide (IIG) as a tonicity agent for use

in intranasal products. Davies and Strang also specifically identified sodium chloride for use in their intranasal naloxone products, with both references disclosing specific concentrations of sodium chloride falling within the claimed range. The Kerr formulation likewise included sodium chloride.

The district court also did not clearly err in finding that the pH of an intranasal formulation is important to avoid nasal irritation, and that the pH—determined through routine optimization—should be somewhere between 3.5 and 7. *Id.* (citing J.A. 3870 (Trial Tr. 347:12–21)). Davies identified a pH of 6.5 and Strang identified a pH of most preferably less than 5.5 (the outer limit of the claimed range) for an intranasal naloxone formulation. And Kerr specifically used hydrochloric acid to adjust the pH of the formulation. Thus, the district court's finding that a skilled artisan would have been motivated to use sodium chloride as a tonicity agent and hydrochloric acid to adjust the pH of the solution as a means to prevent nasal irritation is not clearly erroneous.

Additionally, recognizing that preservatives are commonly used in intranasal formulations, the district court found that the claimed excipient BZK was "commonly used as a preservative and had been used in over 200 intranasal products." *Id.* (first citing J.A. 3905–06 (Trial Tr. 382:11–383:3); then citing J.A. 4299–300 (Trial Tr. 776:20–23, 777:5–8); and then citing J.A. 4557 (Trial Tr. 1034:17–21)). The evidence before the district court supports this fact finding. BZK, like sodium chloride, was listed in the IIG as a commonly used preservative. Kulkarni taught a skilled artisan that BZK had been used in concentrations up to 0.119% w/w, which encompasses the claimed range. And both Davies and Kerr specifically used the claimed excipient BZK as a preservative in their respective intranasal naloxone formulations, with the Kerr formulation using a concentration of BZK falling within the claimed range.

The district court also found that naloxone degradation was known in the prior art, and that the use of a stabilizer, such as the claimed excipient EDTA, prevents naloxone degradation. *Id.* (citing J.A. 3872–73 (Trial Tr. 349:8–350:12)). This was expressly taught in Bahal, which taught a "preferred" concentration of EDTA for stabilizing naloxone that encompasses the claimed range. Bahal col. 2 ll. 65–67. And Kulkarni, similarly, taught a skilled artisan that EDTA should be used in intranasal formulations in concentrations up to 0.5% w/w, which again falls within the claimed range. The district court found that, in view of Bahal's teachings, "a POSA might be motivated to try combining EDTA and BZK" in a naloxone formulation," *Judgment Op.*, 2020 WL 3428078, at *21 (citing Trial Tr. 720:18–721:1, ECF No. 293), because "EDTA could be used with BZK in intranasal formulations to increase their preservative effects," *id.* at *28 (first citing J.A. 4328–29 (Trial Tr. 805:23–806:6); then citing J.A. 3901 (Trial Tr. 378:9–19); and then citing J.A. 3953–54 (Trial Tr. 430:25–431:20)). Given the record evidence supporting its findings, we see no clear error in the district court's findings that a skilled artisan "would have been motivated to select and use BZK as a preservative" and "to select and use EDTA as a stabilizing agent" for use in an intranasal naloxone formulation, particularly given their synergistic interaction. *Id.*

The district court—recognizing that the Aptar UnitDose Device was an already FDA-approved medical device specifically recommended in the prior art for use with drugs that are administered sporadically (like intranasal naloxone)—also found that a skilled artisan would have "been motivated to select the Aptar UnitDose device when developing an improved intranasal naloxone product" as a way of administering intranasal naloxone in lieu of using the MAD Kit. *Id.* at *24. Indeed, at the FDA's 2012 meeting, industry experts discussed the use of a one-step intranasal delivery device for administering

intranasal naloxone. *Id.* at *8 (citing J.A. 3860 (Trial Tr. 337:15–20)). Davies and Strang likewise recognized that a one-step device would be beneficial. We therefore see no clear error in the district court's finding.

Third, the district court found that a skilled artisan would have been motivated to use the claimed 4 mg dose of intranasal naloxone. At the 2012 meeting, "[t]he FDA specifically mentioned that it was curious about the bioavailability of an intranasal naloxone product as compared to the existing intravenous or intramuscular products." *Id.* at *2. The district court found that Strang estimated that "an intranasal dose of 3mg to 4mg would be bioequivalent to the FDA-approved 1mg injectable dose." *Id.* at *29 (first citing J.A. 3916–17 (Trial Tr. 393:20–394:20); and then citing Strang at p. 48). Moreover, the district court noted that using a higher dose of intranasal naloxone would reduce the chances of having to administer a second dose, a consideration it found weighed in favor of using a higher dose in the first instance. We see no clear error in the district court's factual findings on the claimed amount of intranasal naloxone.

Finally, the district court found that a skilled artisan would have been motivated to combine the prior art references to arrive at the claimed invention. *Id.* at *29–31, *42. Here, the "interrelated teachings" of the prior art references support the district court's finding that a skilled artisan would have been motivated to combine the references. *Plantronics*, 724 F.3d at 1354. Take, for example, the Davies combination. As the district court explained, Kerr 2009, like Davies, recognized "the benefits of intranasal naloxone." *Judgment Op.*, 2020 WL 3428078, at *20 (citing J.A. 3927 (Trial Tr. 404:6–15)). And Bahal, although directed to injectable naloxone formulations, discovered that the addition of a stabilizing agent like EDTA to a naloxone formulation prevents naloxone degradation. Therefore, a skilled artisan would have been motivated to combine each of the references in the Davies combination

to arrive at an improved intranasal naloxone product as they are "clearly within a common field of endeavor." *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 978 (Fed. Cir. 2014). Indeed, the district court credited Dr. Smyth's testimony that a skilled artisan would have been motivated to combine each of these references. *See Judgment Op.*, 2020 WL 3428078, at *31 (citing J.A. 3931 (Trial Tr. 408:11–24)).

Turning to the Strang combination, Strang explained that "[t]ypical pharmaceutical excipients used in intranasal formulations are known to the skilled person and can be used for the formulations according to the present invention." Strang at p. 33 ll. 18–20; *see also Judgment Op.*, 2020 WL 3428078, at *28. Dr. Smyth, whose testimony the district court credited, explained that a skilled artisan would have had an apparent reason to combine each of the references in the Strang combination because the details of "the formulation would be filled in through references like Kulkarni" and furthermore "Djupesland specifically points towards the Aptar Unit[D]ose device for the device to be used in an invention like Strang." J.A. 3906 (Trial Tr. 383:4–18); *see also Judgment Op.*, 2020 WL 3428078, at *9 (citing same), *31. As noted above, Kulkarni specifically identifies commonly used excipients for intranasal formulations, excipients which are listed in the FDA's IIG. In view of Strang's teaching that a skilled artisan would have known which excipients could be used with its intranasal naloxone formulations, we see no clear error in the district court's finding that a skilled artisan would have been motivated to look to and modify Strang in view of Kulkarni and Djupesland to develop such a formulation.

We acknowledge, as the dissent notes, that Dr. Smyth did not expressly provide a reason to combine or modify the prior art. *See* Dissent at 10 (stating "Dr. Smyth did not state that the prior art contains a motivation to combine, even when explicitly invited to do so" (citing J.A. 3940 (Trial Tr. 417:13–19)). But this does not warrant reversal.

Since the Supreme Court's decision in *KSR*, we have recognized that an obviousness case does not require expert testimony for every piece of the analysis. *Cf. Wyers v. Master Lock Co.*, 616 F.3d 1231, 1239 (Fed. Cir. 2010) ("*KSR* and our later cases establish that the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." (collecting cases)). As to the specific factual consideration of motivation to combine, the fact finder (here, the district court) is not constrained to an expert's say-so; other documentary evidence, such as the teachings of the prior art or problems known in the field of endeavor at the time of the invention, can provide the requisite support for the court's motivation finding. *Plantronics*, 724 F.3d at 1354; *KSR*, 550 U.S. at 418–19. As explained in detail above, the district court did not rely solely on Dr. Smyth's summary testimony in finding that there would have been a motivation. The evidence of record the district court considered included the known drawbacks to the MAD Kit, the express guidance from the FDA, and the teachings of the prior art references themselves. This is sufficient support for the district court's motivation finding. We are certainly not left with the definite and firm conviction that the district court erred in so finding.

The dissent also claims that there was "no suggestion in the prior art to select th[e] specific combination and concentration of components" claimed in the patents-in-suit. Dissent at 5. In so stating, the dissent quotes testimony from Dr. Smyth as suggesting that it would have been obvious to "pick" the claimed excipients simply because they were "available." Dissent at 5–6 (citing J.A. 3938 (Trial Tr. 415:9–12)). Whatever inference can be drawn from this small slice of Dr. Smyth's testimony, the fact remains that the prior art itself wholly undermines the dissent's assertions. First, the asserted references provide exemplary formulations comprising naloxone in combination with one or more of the claimed excipients. *E.g.*, Davies, Example 1

(describing intranasal naloxone composition formulated with BZK); J.A. 11467 (Kerr intranasal naloxone formulation comprising sodium chloride, BZK, and pH adjusted with hydrochloric acid); Bahal col. 1 ll. 53–54 (describing benefit of using EDTA in combination with naloxone to prevent degradation). It is of no moment that no single reference discloses naloxone in combination with all of the claimed excipients, as Teva's invalidity case was based on obviousness, not anticipation. And the district court provided ample rationale, supported by record evidence, for why a skilled artisan would have been motivated to use each of the claimed excipients in combination with naloxone. *See Judgment Op.*, 2020 WL 3428078, at *28–31. Second, as detailed above, the prior art likewise describes concentrations for each of the excipients falling within or encompassing the claimed ranges. In view of these explicit teachings in the prior art, we see no clear error in the district court's finding (crediting Dr. Smyth's testimony) that arriving at the claimed concentration range for each of the well-known excipients would have required no more than routine optimization. *See id.*

Thus, looking at the district court's analysis as a whole and the record evidence relied on throughout its analysis, we hold that the district court's finding that a skilled artisan would have been motivated to combine the asserted prior art references to arrive at the claimed invention is not clearly erroneous.[10]

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[10] The dissent characterizes the majority holding as based solely on "the known need for a better product." Dissent at 9. That is not a correct characterization. As explained in detail, the published need to improve upon the MAD Kit is but one of several facts supporting the district court's finding that there would have been a motivation to combine.

II

We turn next to the district court's finding that the prior art, as a whole, did not teach away from the claimed invention. At trial, Adapt argued that the Wyse reference,[11] which was not relied on in any of the prior art combinations Teva presented, taught away from using BZK as a preservative. The district court, after considering the prior art of record as well as the testimony of both parties' experts, found otherwise. *Judgment Op.*, 2020 WL 3428078, at *31–32, *42–43. On appeal, Adapt asserts that the district court applied the wrong legal standard in its analysis, and that, under the correct standard, Wyse teaches away from the claimed invention. We disagree.

Wyse—which published on June 25, 2015, after the priority date of the patents-in-suit—describes a screening study conducted on various excipients for use in intranasal naloxone formulations. Wyse, Example 5. This screening study was designed to accelerate degradation of naloxone to assess compatibility of each excipient. BZK was one of the tested excipients and was included in a number of the formulations—formulations 7, 9, 12, 14, and 14A—at a concentration of 0.125% w/v. *Id.* Tbl. 13. This concentration is 8.5 times greater than the concentration of BZK claimed in the patents-in-suit. Wyse observed that "the use of [BZK], a common nasal product preservative, resulted in an additional degradant in formulations 7, 9, 14, and 14A." *Id.* at col. 27 ll. 29–32. Although Wyse concluded that BZK was not acceptable for use in an intranasal naloxone formulation "due to increased observed degradation," *id.* at col. 27 ll. 41–44, Dr. Smyth testified that a skilled artisan reading Wyse would not have been dissuaded from using BZK at all in an intranasal naloxone formulation, only from using such high concentrations:

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[11] U.S. Patent No. 9,192,570.

> Q. So what kind of conclusion would a POSA have drawn about the use of [BZK] from Wyse?
>
> A. That you shouldn't use a high concentration of [BZK]. That may cause naloxone degradation.
>
> Q. Would a POSA have been dissuaded from using [BZK] altogether?
>
> A. Not in my opinion.

J.A. 3949 (Trial Tr. 426:13–19). The district court credited this testimony and ultimately afforded Wyse's conclusion little weight in finding that the prior art did not teach away from using the claimed amount of BZK in an intranasal naloxone formulation. *Judgment Op.*, 2020 WL 3428078, at *32 (citing J.A. 3949 (Trial Tr. 426:13–19)).

Adapt contends that, in analyzing Wyse, the district court failed to apply the proper legal standard regarding teaching away—a "reference teaches away if a POSA 'upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'" Appellants' Br. 40 (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). But the corollary is equally true and particularly fitting here: a reference does not teach away if a skilled artisan, upon reading the reference, would *not* be "discouraged from following the path set out in the reference," and would *not* be "led in a direction divergent from the path that was taken by the applicant." The district court specifically credited Dr. Smyth's testimony that a skilled artisan would *not* have been dissuaded from using BZK in an intranasal naloxone formulation, only from using the high concentrations tested in Wyse. This factual finding is supported by expert testimony and consistent with our precedent and the standard that Adapt argues the district court failed to apply. We therefore discern no clear

error in the district court's decision to afford less weight to Wyse's findings in its teaching away analysis.

At oral argument on appeal, Adapt asserted that the district court's legal error was one of omission—its failure to cite the teach away standard in its opinion—not that the district court articulated an incorrect standard. Oral Arg. at 8:45–10:42, http://oralarguments.cafc.uscourts.gov/default.aspx?fl=20-2106_08022021.mp3. Federal Rule of Civil Procedure 52(a), however, requires only that a district court "find the facts specially and state its conclusions of law separately." It does not require the district court to specifically articulate the legal standard it is applying in coming to its legal conclusion. Moreover, we review judgments, not opinions. *Advanced Steel Recovery, LLC v. X-Body Equip., Inc.*, 808 F.3d 1313, 1321 (Fed. Cir. 2015); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983). And at any rate, the district court did rely on relevant teaching-away precedents. *Judgment Op.*, 2020 WL 3428078, at *42 (first citing *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); then citing *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); and then citing *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381 (Fed. Cir. 2017)). As explained above, we determine that the district court's legal conclusion is proper in light of this court's precedent and the evidence presented.

Furthermore, the district court properly analyzed Adapt's contention that Wyse taught away in the context of the other prior art of record and based on the knowledge of a skilled artisan established by the expert testimony. As the district court correctly observed, "there is no rule that a single reference that teaches away will mandate a finding of nonobviousness." *Judgment Op.*, 2020 WL 3428078, at *42 (quoting *Medichem*, 437 F.3d at 1165). "Rather, the prior art must be considered *as a whole* for what it teaches." *Medichem*, 437 F.3d at 1166.

Here, the district court found it relevant that Davies and the Kerr formulation taught the use of BZK specifically in intranasal naloxone formulations at concentrations similar to the claimed concentration, and that the prior art did not express "any concerns" with the stability of these formulations. *Judgment Op.*, 2020 WL 3428078, at *32. On this point, the district court once again credited Dr. Smyth's testimony that a skilled artisan would have, therefore, inferred that these formulations were stable. *Id.* (citing J.A. 4809–11 (Trial Tr. 1282:18–1284:11)). The district court also found it relevant that "BZK is perhaps the most commonly used . . . preservative in nasal formulations," relying on the following testimony from Dr. Smyth:

> Q. . . . So would a POSA, after reading Wyse, be dissuaded from using [BZK] and naloxone formulation?
>
> A. No.
>
> Q. And why not?
>
> A. Because [BZK] had been used in the prior art with naloxone successfully. [BZK] is the most commonly used preservative in nasal sprays. I'm sure they would have studied it further.

Id. at *31 (citing J.A. 4808 (Trial Tr. 1281:16–24)). In view of the evidence presented at trial, the district court found "that the prior art as a whole did not teach away from using BZK with naloxone." *Id.* at *32; *see also id.* at *42–43. We discern no clear error in the district court's finding.

The district court, sitting as the fact finder, was entitled to consider the teachings of the prior art as a whole in finding that the prior art did not teach away from the claimed invention. Because the district court did not apply an incorrect legal standard and its factual findings are well-supported by the evidence of record, it is not our role, as an appellate court, to disturb the district court's weighing of that evidence on appeal.

III

Finally, we consider Adapt's argument that the district court erred in its analysis of the objective indicia of nonobviousness. Objective indicia "must always when present be considered" in the overall obviousness analysis. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.* (*BMS*), 752 F.3d 967, 977 (Fed. Cir. 2014) (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1075–76, 1079 (Fed. Cir. 2012)). But "they do not necessarily control the obviousness determination." *Id.* at 977. Indeed, "a strong showing of obviousness may stand 'even in the face of considerable evidence'" of objective indicia. *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1374 (Fed. Cir. 2018) (quoting *Rothman v. Target Corp.*, 556 F.3d 1310, 1322 (Fed. Cir. 2009)).

As a preliminary matter, we address Adapt's argument, relying on *In re Cyclobenzaprine*, that the district court committed legal error because, according to Adapt, it concluded that the asserted claims would have been obvious before considering Adapt's evidence of objective indicia of nonobviousness. We are not persuaded. In *In re Cyclobenzaprine*, we held that the district court erred by failing to "consider all evidence relating to obviousness before finding a patent invalid" when it reached the ultimate legal conclusion "that the patents in suit were obvious before it considered the objective considerations." 676 F.3d at 1075. Here, by contrast, it is evident from the district court's opinion that it considered all of the evidence on the issue of obviousness, including the objective indicia of nonobviousness, in coming to its ultimate legal conclusion. Although the district court's analysis of the objective indicia in the opinion follows its discussion of the prima facie case of obviousness, there is nothing inherently wrong with that. *KSR*, 550 U.S. at 399 ("While the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry."); *e.g.*, *id.* at 426 ("Teleflex has shown no secondary factors to dislodge the

determination that claim 4 is obvious."); *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1199 (Fed. Cir. 2014) ("[The patentee] first objects to the fact that the district court turned to these indicia only after concluding that [it] 'has proved by clear and convincing evidence a prima facie case of obviousness.' We are unpersuaded that the legal framework employed by the district court was improper." (citation omitted)).

Moreover, the district court's substantive analysis of this evidence spans over twenty pages. As we explain in detail below, the district court's analysis was "*part of* the whole obviousness analysis, not just an afterthought" to a forgone legal conclusion. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357–58 (Fed. Cir. 2013). Rather, "it is clear that the district court did consider the objective indicia before reaching its ultimate obviousness conclusion, which is what our precedent counsels." *PAR*, 773 F.3d at 1199.

Having found no procedural error in the district court's treatment of Adapt's proffered objective indicia, we turn to the merits. Adapt argues that its evidence of unexpected results, copying, skepticism, long-felt need, and failure of others mandates a conclusion of nonobviousness. The district court rejected these arguments. We address each indicium in turn.[12]

A

We begin with Adapt's assertion that the claimed formulations exhibited unexpected results compared to the

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[12] We limit our review of the objective indicia to Adapt's legal and factual challenges on appeal. We will not reweigh the evidence on appeal, as the dissent would prefer. Dissent at 14 (asserting that we do not "give fair weight to the objective indicia in this area of public concern"). As an appellate court, that is not our role.

closest prior art formulation—a formulation developed by AntiOp, Inc. based on the formulation described in Wyse's Table 1 (the "AntiOp formulation"). "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *BMS*, 752 F.3d at 977. Here, the district court considered the evidence Adapt presented—namely, that the claimed formulations exhibited (1) an unexpected increase in bioavailability and (2) unexpected stability—and found, "[i]n light of the testimony given at trial and the exhibits entered into evidence," that this was not "evidence of unexpected results" probative of nonobviousness. *Judgment Op.*, 2020 WL 3428078, at *34. This finding is not clearly erroneous.

First, the district court found that Adapt's evidence that NARCAN®—which the parties agree is an embodiment of the asserted claims—has a 56% increase in bioavailability compared to the AntiOp formulation was not an unexpected result probative of nonobviousness. *Id.* at *33; *see also* J.A. 4287 (Trial Tr. 764:17–22). The district court noted that the AntiOp formulation differs from the claimed formulations in that the AntiOp formulation includes citric acid and benzyl alcohol but does not use BZK. *Compare* Wyse Tbl. 1, *with* '747 patent col. 53 ll. 8–29; *see also Judgment Op.*, 2020 WL 3428078, at *33. The district court then credited Dr. Smyth's testimony that a skilled artisan would have *expected* that using BZK—as in the claimed formulations—would increase the relative bioavailability of the formulation because BZK was a known permeation enhancer that "cause[s] a drug to permeate more readily across a

membrane."[13] *Judgment Op.*, 2020 WL 3428078, at *33 (first citing J.A. 4796–97 (Trial Tr. 1269:24–1270:11); and then quoting J.A. 4797 (Trial Tr. 1270:16–29)); *see also id.* at *44. The district court, having considered this and other testimony of record, found that a skilled artisan would have therefore expected that using a permeation enhancer such as BZK would result in increased bioavailability compared to a formulation without a permeation enhancer, such as the AntiOp formulation, and thus the increase in bioavailability was not an "unexpected" result. We see no clear error in the district court's finding. *See BMS*, 752 F.3d at 977–78 (finding no clear error in district court's fact finding that "entecavir's 'effectiveness against hepatitis B without known toxicity issues' was '*not unexpected*,'" and deferring to district court's finding that this was not sufficient evidence of nonobviousness).

Adapt argues that the district court's finding is contrary to this court's decision in *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265 (Fed. Cir. 2018). Appellants' Br. 51. We disagree. In *Orexo*, we held that the district court erred in discounting an unexpected 66% increase in bioavailability as a difference in degree, not kind. 903 F.3d at 1274. We explained that such an *unexpected* increase in bioavailability is a difference in kind that is probative of nonobviousness, not a trivial difference in degree. *Id.* Unlike this case, however, in *Orexo* there was no evidence before the district court that a skilled artisan would have had reason to *expect* a significant increase in bioavailability compared to the closest prior art. Here, the district court was presented with and entitled to weigh evidence that a skilled artisan would have, in fact, expected a

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[13] Contrary to the dissent's assertion, this testimony establishes that the "unexpected" biological activity was not "undisputed." Dissent at 13.

bioavailability increase when considering whether Adapt's evidence showed an "unexpected result." *Orexo* is inapplicable here.

The district court also considered Adapt's argument that the claimed formulations are unexpectedly stable because Wyse, which reported increased degradation when BZK was used in intranasal naloxone formulations, taught away from using BZK. Appellants' Br. 52–53. The district court found this argument "unconvincing," based largely on its finding that the formulation in Wyse used a much higher concentration of BZK than is claimed in the patents-in-suit, as well as its finding that the prior art, including Wyse, did not teach away from using BZK. *Judgment Op.*, 2020 WL 3428078, at *34. We see no clear error in the district court's finding that the claimed formulations are not unexpectedly stable, particularly in light of our conclusion above that the district court's finding that Wyse does not teach away from the claimed invention is not clearly erroneous.

Based on the evidence presented at trial, we hold that the district court did not clearly err in its factual findings regarding a lack of unexpected results. Accordingly, we see no error in the district court's decision to afford this evidence little weight in its overall obviousness analysis. *See id.* at *44 (finding "that Adapt has [not] presented significant evidence of unexpected results"); *see also id.* at *34.

B

We turn next to Adapt's argument that the district court erred in its analysis of Adapt's evidence of alleged copying of the claimed 4 mg dose. At trial, Adapt presented evidence that Mundipharma International Ltd. changed its formulation to copy the 4 mg dose after the patents-in-suit were published, and that another product known as Ezvio, an intramuscular injectable product, later increased the dose of its product to 2 mg. The district court considered

this evidence and found Adapt's assertion of copying "unconvincing." *Judgment Op.*, 2020 WL 3428078, at *47.

Adapt also presented evidence that Teva, like Mundipharma, changed its formulation to the claimed 4 mg dose, arguing that this was evidence of copying probative of nonobviousness. But we have held that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *see* J.A. 3594–95 (Trial Tr. 71:19–72:6) (Teva's fact witness explaining that a generic company is required to "use the same amount of naloxone" or "it's not bioequivalent"). The district court recognized this principle and accordingly discounted evidence that Teva copied the NARCAN® formulation as non-probative. *Judgment Op.*, 2020 WL 3428078, at *46–47.

We see no clear error in the district court's findings. We therefore will not reweigh this evidence or second guess what may or may not have been convincing evidence of copying probative of nonobviousness to the district court. *See id.* at *37 (finding there was not "significant evidence of copying" probative of nonobviousness).

C

We also consider Adapt's argument that the district court erred in its analysis of industry skepticism—specifically, skepticism concerning the 4 mg dose of intranasal naloxone. Adapt's expert, Dr. Kenneth A. Williams, testified that there was concern surrounding the potential for severe withdrawal if doses of intranasal naloxone higher than 2 mg were administered to an overdose patient. Dr. Williams also testified that he does not recommend the use of NARCAN® for use in an EMS system because of its high dose of naloxone (4 mg). The district court, after considering this testimony, found that "these concerns [were] not sufficiently substantial to constitute objective indicia of

nonobviousness." *Judgment Op.*, 2020 WL 3428078, at *37; *id.* at *47. We discern no clear error in this finding.

Contrary to Adapt's assertion, the district court did not "g[i]ve this consideration no weight." Appellants' Br. 53. The district court gave this evidence the weight it deemed appropriate in light of the evidence introduced at trial. Importantly, the district court did not consider Adapt's evidence in a vacuum; additional evidence was introduced that the district court, sitting as fact finder, reasonably relied on in considering whether the industry as a whole was skeptical of using a 4 mg dose of intranasal naloxone. For example, the district court found relevant the FDA's statements (1) recommending that Lightlake consider a higher dose of naloxone than its contemplated 2 mg dose and (2) that it would be "acceptable" if a higher dose of naloxone was needed to achieve similar bioavailability to the approved intramuscular product. *Judgment Op.*, 2020 WL 3428078, at *38, *47. We therefore reject Adapt's argument and hold that that the district court did not clearly err in finding that Adapt's evidence of industry skepticism is not significantly probative of nonobviousness.

D

Finally, we turn to Adapt's argument that the district court clearly erred in finding that there was no long-felt but unmet need for a needle-free and easy-to-use intranasal naloxone product. Although, as explained below, we agree that the district court erred in its analysis, we conclude that this error was harmless because the evidence Adapt introduced is not sufficient to overcome the strong case of obviousness as a matter of law.

The district court's long-felt-need analysis focused almost entirely on the MAD Kit. As explained above, the MAD Kit—which combined an injectable naloxone product with the MAD device that allowed the naloxone formulation to be sprayed into a nostril—had a number of known drawbacks and disadvantages. Recognizing this, the

district court reasoned that a skilled artisan would have been motivated to improve upon these drawbacks to arrive at the claimed invention. Indeed, as explained above, the FDA in 2012 specifically sought to improve upon the MAD Kit, encouraging the industry to develop an intranasal naloxone product. *See* J.A. 3859–60 (Trial Tr. 336:11–15, 336:21–337:3). Adapt succeeded in developing such a product, and the FDA "fast track[ed]" Adapt's NDA, which is a process that is reserved for drugs that "treat serious conditions and fill an unmet medical need." J.A. 4994–95 (Trial Tr. 1467:1–5, 1467:24–1468:4). After considering this evidence, the district court found that "[w]hile [NARCAN®] may be an improvement over the MAD Kit," it nevertheless "did not fill a significant long-felt but unmet need," *Judgment Op.*, 2020 WL 3428078, at *37, because, among other reasons, the MAD Kit was "known to be safe and effective," *id.* at *46.

To the extent the district court was suggesting that there was no long felt but unmet need because any "need" was met by the prior art MAD Kit, this was error. Indeed, we fail to see how, on the one hand, the MAD Kit and its known drawbacks can provide a skilled artisan with the motivation to arrive at the claimed invention and, on the other hand, satisfy an unmet need in the prior art.

But even if we give Adapt's evidence of long-felt need the weight that Adapt urges, we nonetheless conclude that it is not sufficient to overcome the strong case of obviousness. *ZUP*, 896 F.3d at 1374. At best, the asserted "long-felt need" here, as most strongly evidenced by the FDA's statements in 2012, began just three years before the priority date of the patents-in-suit. This need, even if unmet, was not so long felt that it overcomes the strong case of obviousness, particularly in view of the plethora of prior art references discussed above identifying "intranasal naloxone as a viable means for treating opioid overdose." *Judgment Op.*, 2020 WL 3428078, at *46. Thus, while the

district court erred in its long-felt-need analysis, we hold that this error was harmless.

We also consider Adapt's argument that others tried, but failed, to arrive at the claimed invention, as this inquiry often goes hand-in-hand with the long-felt need inquiry. *See, e.g.*, *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017) ("Evidence of long-felt need is 'particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.'" (quoting *In re Cyclobenzaprine*, 676 F.3d at 1082–83)). Specifically, Adapt argues that the district court clearly erred in dismissing evidence that other companies tried and failed "to develop an effective, safe, and easy-to-use product that is FDA-approved." Appellants' Br. 49. We disagree.

Adapt presented evidence that a number of companies sought FDA approval for their products but were ultimately rejected. This included (1) the AntiOp formulation; (2) the Mundipharma formulation; and (3) Amphastar Pharmaceuticals' attempt to obtain FDA approval for the MAD Kit. The district court, after considering this evidence, found that the alleged failure of others here was "not a significant indici[um] of nonobviousness." *Judgment Op.*, 2020 WL 3428078, at *36. As to the AntiOp formulation, the district court explained that, though this product had not received FDA approval, it was "approved in other countries." *Id.* at *36; J.A. 4333–34 (Trial Tr. 810:25–811:4). The same was true for Mundipharma's formulation. J.A. 4333–34 (Trial Tr. 810:25–811:4). The district court weighed that evidence accordingly. We are not left with a definite and firm conviction that the district court erred in this regard. We thus see no clear error in the district court's finding that this evidence is not significantly probative of nonobviousness.

Nor are we persuaded that Amphastar's failure to obtain FDA approval for the MAD Kit is particularly probative of nonobviousness. Indeed, as the district court recognized, the MAD Kit is "widely used . . . to treat opioid overdoses," despite not being FDA approved. *Judgment Op.*, 2020 WL 3428078, at *36; *see also id.* at *46. The district court, as fact finder, was entitled to weigh the lack of FDA approval together with evidence of the MAD Kit's widespread use and find that the lack of approval was not a significant indicium of nonobviousness. Because we see no clear error in the district court's factual findings, we will not disturb this weighing of the evidence on appeal.

CONCLUSION

This is a close case, with facts supporting both parties' arguments as to their preferred outcome. But we are a court of review, not a court of first resort, and our review of the district court's judgment is accordingly limited. This is particularly true when reviewing challenges to the district court's factual findings, to which we give great deference absent clear error. After a two-week bench trial in which it reviewed the evidence of record and considered the testimony of numerous fact and expert witnesses, the district court determined that the asserted claims would have been obvious. We have considered all of Adapt's challenges to the district court's factual findings on appeal, but we see no basis to disturb the district court's ultimate legal conclusion of obviousness. We therefore affirm the district court's judgment that the asserted claims are invalid as obvious.

AFFIRMED

United States Court of Appeals for the Federal Circuit

ADAPT PHARMA OPERATIONS LIMITED, ADAPT PHARMA, INC., ADAPT PHARMA LIMITED, OPIANT PHARMACEUTICALS, INC.,
Plaintiffs-Appellants

v.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES, LTD.,
Defendants-Appellees

2020-2106

Appeal from the United States District Court for the District of New Jersey in Nos. 2:16-cv-07721-BRM-JAD, 2:17-cv-00864-JLL-JAD, 2:17-cv-02877-JLL-JAD, 2:17-cv-05100-JLL-JAD, 2:18-cv-09880-JLL-JAD, Judge Brian R. Martinotti.

NEWMAN, *Circuit Judge*, dissenting.

This appeal concerns the patentability of Adapt Pharma's new method of treatment of opioid overdose. The claimed method solves the previously unmet needs of enhanced efficacy and ease of administration of the known medication naloxone. Patentability is challenged under the provisions of the Hatch-Waxman Act.

The claimed method concerns the product having the brand name Narcan® whose active ingredient is naloxone. The claimed method is reported by the Food & Drug Administration ("FDA") to deliver 56% more naloxone into the bloodstream compared with the closest prior art. Adapt Pharma states that "Narcan became 'the first and only' FDA-approved naloxone intranasal spray," and it "captured over 95% of the retail market." Adapt Br. 11.

Nonetheless, the court now holds that this new method was obvious. The court's ruling is contrary to the law of section 103, for there was no teaching or suggestion in the prior art to make this combination of ingredients for use in the claimed method to achieve the described beneficial results.

I respectfully dissent.

DISCUSSION

The only issue is obviousness

The only issue is obviousness, 35 U.S.C. § 103. The district court[1] treated claim 9 of U.S. Patent No. 9,468,747 as representative, shown with the claims from which it depends:

> **1.** A method of treatment of opioid overdose or a symptom thereof, comprising nasally administering to a patient in need thereof a dose of naloxone hydrochloride using a single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient, having a single reservoir comprising a pharmaceutical composition which is an aqueous solution of about 100 µL comprising:

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[1] *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, Case No. 2:16-cv-7721 (BRM) (JAD), 2020 WL 3428078 (D.N.J. June 22, 2020) ("Dist. Ct. Op.").

> about 4 mg naloxone hydrochloride or a hydrate thereof;
>
> between about 0.2 mg and about 1.2 mg of an isotonicity agent;
>
> between about 0.005 mg and about 0.015 mg of a compound which is at least one of a preservative, a cationic surfactant, and a permeation enhancer;
>
> between about 0.1 mg and about 0.5 mg of a stabilizing agent; and
>
> an amount of an acid sufficient to achieve a pH of 3.5–5.5.
>
> **2.** The method as recited in claim 1 wherein:
>
> the isotonicity agent is NaCl;
>
> the preservative is benzalkonium chloride;
>
> the stabilizing agent is disodium edetate; and
>
> the acid is hydrochloric acid. . . .
>
> **4.** The method of claim 2, wherein said method is actuatable with one hand.
>
> **5.** The method of claim 4, wherein the volume of said reservoir is not more than about 140 µL.
>
> **6.** The method of claim 5, wherein about 100 µL of said aqueous solution in said reservoir is delivered to said patient in one actuation.
>
> **7.** The method of claim 6, wherein the pharmaceutical composition which is an aqueous solution comprises about 4.4 mg naloxone hydrochloride dihydrate. . . .
>
> **9.** The method of claim 7, wherein the 95% confidence interval for dose delivered per actuation is ±about 2.5%.

'747 patent, col. 53, ll. 8–51.

As the patented invention is summarized by Adapt Pharma, "its unique features include its pre-primed device,

administered intranasally, providing a single 4mg dose, together with its specific combination of excipients at particular concentrations. This unique formulation delivers 56% more naloxone to the bloodstream of patients relative to the next most similar formulation . . .” Adapt Br. 10–11. The greatly improved performance and other advantages are not disputed.

Adapt Pharma recites the failures of others to meet the known need of providing an effective opioid overdose treatment. The need had become so pressing that the FDA “held a public meeting . . . to encourage the industry to ‘develop an intranasal naloxone product that could be FDA approved.’” Dist. Ct. Op. at *8. The primary products then available to administer naloxone were the Mucosal Atomization Device (the “MAD Kit”) for nasal inhalation, and the Evzio auto-injector for needle injection. The district court recited the inadequacies of these devices and treatments. Dist. Ct. Op. at *16, *23–24. The marked superiority of the Adapt Pharma method and product is not disputed.

Adapt Pharma advises that three other entities, Amphastar, Mundipharma, and AntiOp, responded to the FDA concern about treatment for opioid overdose. Adapt Br. 9–10. Amphastar and AntiOp’s methods were rejected by the FDA, *see id.* (citing Appx5422, 5425–5426), and Mundipharma never sought FDA approval. Appx5426.

Narcan® met a long-felt need upon failure of others, and is a successful medicinal product that defendant Teva and others seek to copy. The FDA fast-tracked its review and approval of Narcan® when its favorable properties became apparent. Nonetheless, the district court held that this new product and method were obvious, and the ’747 patent was held invalid.

The prior art has no teaching or suggestion of the claimed method

All of the components of the Narcan® composition were separately known. *See* Dist. Ct. Op. at *14 (discussing testimony of Adapt expert Dr. Soumyajit Majumdar). However, the specific combination of components and concentrations described and claimed in the '747 patent was not known or suggested in the prior art, while the extent of improvement achieved in treatment of opioid overdose was striking, providing rapid enhanced effectiveness combined with ease of administration. *See Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) ("Where, as here, the necessary reasoning is absent, we cannot simply assume that an ordinary artisan would be awakened to modify prior art in such a way as to lead to an obviousness rejection. It is in such circumstances, moreover, that it is especially important to guard against the dangers of hindsight bias." (internal quotation marks and citation omitted)). Here too, the only suggestion of the '747 method is found in the '747 patent itself.

The panel majority holds that it was obvious to make this invention, although the majority cites no teaching or suggestion to do so. Although Teva's expert Dr. Hugh Smyth testified that this new method and composition were obvious to him, he could point to no suggestion in the prior art to select this specific combination and concentration of components. Instead, he simply stated that since the components were "available," in his opinion it was obvious to make the selection of components and concentrations that Adapt Pharma made. *See* Smyth Testimony, Trial Tr. 415:9–12:

> Q. And how would a person of skill in the art pick a value out of that range?

> A. They could pick any value out of that range that would be available to a person of ordinary skill to look at.

Dr. Smyth's testimony is Teva's only support for its argument of obviousness, but Dr. Smyth never stated that the specific combination and amounts of components in claim 9 is described or suggested in the prior art. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1351 (Fed. Cir. 2014) (defendant's expert "failed to provide the necessary 'articulated reasoning with some rational underpinning' to support a conclusion of invalidity based on [the proposed] combinations." (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007))).

The record contains no support for the district court's finding that "a skilled artisan would have been motivated to look to and modify Strang in view of Kulkarni and Djupesland to develop such a formulation," Maj. Op. at 19 (citing references disclosing various components). This is a classical example of judicial hindsight, where the invention itself is the only guide to the selections from the prior art.[2]

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[2] The panel majority endorses the district court's analysis of the motivation to select and combine the specified components from various references. Maj. Op. at 12–21. The district court, like expert Dr. Smyth, identifies no teaching or motivation in the prior art to make the claimed selection and thereby to achieve the unexpected properties of the '747 invention. Instead, the district court finds the teaching and motivation in the '747 patent itself. *See* Dist. Ct. Op. at *28 ("The pH of an intranasal product is commonly adjusted and can be optimized with repeated experimentation. The Court finds, therefore, that a POSA would have used hydrochloric acid to adjust the pH of a nasal formulation."). However, existence of the separate elements does not establish the motivation to select and combine them to produce the claimed invention. *See In re Van Os*, 844 F.3d 1359, 1361 (Fed. Cir. 2017).

The district court reconstructed the Adapt Pharma method and composition from the teachings of the patents in suit, not from the prior art. My colleagues now adopt the district court's flawed reasoning.

In addition, the panel majority holds that the enhanced benefits of this new method and composition were expected, thus negating nonobviousness. *See* Maj. Op. at 28 ("The district court, having considered this and other testimony of record, found that a skilled artisan would have therefore expected that using a permeation enhancer such as BZK would result in increased bioavailability compared to a formulation without a permeation enhancer, such as the AntiOp formulation, and thus the increase in bioavailability was not an 'unexpected' result. We see no error in the district court's finding."). However, we are directed to no teaching or suggestion to make this combination. To the contrary, the prior art teaches that BZK degrades naloxone.

The Wyse reference states that those inventors ceased experimentation with BZK and naloxone upon discovering BZK's degradation of naloxone; the reference states that while other preservatives "were acceptable" for use in combination with naloxone, BZK "was not, due to increased observed degradation." Wyse, U.S. Patent No. 9,192,570, col. 27, ll. 43–44. Dr. Smyth agreed that a skilled artisan seeking to make an intranasal naloxone product would strive for "robust stability." Smyth Testimony, Trial Tr. 1292:9–18. Dr. Smyth also agreed that "[g]enerally, you try and make your formulation as stable as possible to give it a longer shelf life, particularly if you are making a product." Smyth Testimony, Trial Tr. 449:16–22.

It cannot be found that the prior art provided a reasonable expectation of success in use of BZK in this naloxone composition, when the prior art explicitly warned that BZK causes unacceptable naloxone degradation. As stated in

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293 (Fed. Cir. 2015):

> [T]he prior art did not disclose, either explicitly or implicitly, the claimed formulation; rather, it taught away from such a formulation. A person of ordinary skill in the art thus would not have had a reason to select the claimed formulation from the prior art ranges or to modify [prior art formulation] to arrive at the claimed formulation. The unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness.

Id. at 1307. The skilled artisan is expected to know when "the prior art warned that risks were involved in using" certain elements from the prior art, *KSR*, 550 U.S. at 416, thus teaching away from use of those elements.

My colleagues simply take the new composition described in the patent, find the several components in various pieces of prior art, and hold that it was obvious to select the specific components and concentrations of claim 9 from the myriad possible combinations of elements. The references that the majority cites show how thoroughly naloxone has been studied, yet no reference suggests this specific combination and its remarkably superior efficacy combined with ease of administration. As stated in *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013):

> This court and obviousness law in general recognizes an important distinction between combining known options into "a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, and "merely throwing metaphorical darts at a board in hopes of arriving at a successful result."

Id. at 1357 (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1075

(Fed. Cir. 2012). "To have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (internal alterations omitted)).

The panel majority observes that to arrive at the claimed invention, the skilled artisan was required to:

> (1) formulate an intranasal naloxone product that would improve upon the MAD Kit; (2) select the claimed excipients—sodium chloride, BZK, EDTA, and hydrochloric acid for adjusting the pH—and the Aptar UnitDose device for intranasal delivery; (3) select a 4 mg dose of naloxone; and (4) combine the prior art references themselves.

Maj. Op. at 12. The majority errs in concluding that the existence of the separate components suffices to find obviousness of this specific combination. The selection of specific ingredients from the prior art is not obvious when "that same prior art gave no direction as to which of the many possible combination choices were likely to be successful." *Leo*, 726 F.3d at 1357.

It is not disputed that the Adapt Pharma method and composition are not shown or suggested in any reference. However, my colleagues hold that the known need for a better product provided the "motivation" element of obviousness. Maj. Op. at 13 (approving of the district court's finding that the skilled artisan would have recognized "the known drawbacks of the MAD Kit and the need for an intranasal naloxone product"). The artisan's knowledge that the available products are deficient does not render the remedy obvious when it is eventually discovered. A

motivation to improve a product does not render the successful improvement obvious.[3]

Several references describe naloxone nasal delivery systems that were deemed inadequate. *E.g.*, the Strang reference, WO 12/156317, Appx6935 and the Davies reference, WO 00/62757, Appx11508. No reference shows all the components and concentrations of the '747 claims, and it is not disputed that the Adapt Pharma product has properties and benefits not provided by a prior art product. The extensive past study of related systems, and the failure to achieve successful results, is evidence of non-obviousness.

Only judicial hindsight purports to create the effective product herein. In *TQ Delta, LLC v. CISCO Systems, Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019), this court cautioned against "allowing the challenger to use the challenged patent as a roadmap to reconstruct the claimed invention using disparate elements from the prior art—i.e., the impermissible *ex post* reasoning and hindsight bias that *KSR* warned against."

The district court relied on Dr. Smyth's testimony to find a motivation to select and combine the specific elements of claim 9. However, Dr. Smyth did not state that the prior art contains a motivation to combine, even when explicitly invited to do so by counsel for Teva. Instead, he

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[3] The panel majority criticizes this analysis, stating at n. 10 that the known need to improve on the MAD Kit provided the motivation to make the claimed combination, alongside Dr. Smyth's testimony and the cited references themselves. However, neither Dr. Smyth's testimony, nor the cited references, teaches or suggests the specific combination of Narcan®. Knowledge that prior art products are deficient is evidence of long-felt need and failure of others, not evidence of obviousness.

simply reiterated that the various components were known:

> Q. . . . So can you sum up for us why a POSA would have arrived at the subject matter of the asserted patents by looking at the combination of Davies, Kerr, and Bahal?
>
> A. So Davies and Kerr provide the examples of intranasal naloxone diluted to treat opioid overdose. Davies and Kerr also have formulation components, as well as Bahal, which provides the EDTA for the stability.

Smyth Testimony, Trial Tr. 417:13–19. Like the district court and the panel majority, Dr. Smyth does not explain why the skilled artisan would have selected these components and concentrations. Precedent is clear that a "general motivation" does "not suffice," for "[a]ny compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharms. Ltd. v. UCB Pharma GmBH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

The lack of motivation is especially acute where, as here, the various components were known to the art, yet the prior art compositions were failures, and a significant ingredient was described as not acceptable for use with naloxone. Wyse, col. 27, ll. 38–44. This description of BZK is the epitome of "teaching away."

The district court misapprehended the law, as does the panel majority. The district court relied on *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157 (Fed. Cir. 2006), where the prior art taught that the addition of a specific compound in a claimed reaction sometimes improved the yield, leading to the ruling that when "a given course of action often has simultaneous advantages and disadvantages," "this does not necessarily obviate motivation to combine." *Id.* at

1165. Citing *Medichem*, the district court found motivation to select and combine all the components of claim 9, despite the known degradation due to BZK.

As observed *ante*, the use of BZK was known to degrade naloxone; it was not ever known to be especially beneficial in this context, merely "common." *See* Wyse, col. 27, ll. 29–32 ("The results further surprisingly showed that the use of benzalkonium chloride, a common nasal product preservative, resulted in an additional degradant . . . ."). The majority departs from rational analysis in holding that although BZK was a known degradant, its use rendered this new naloxone composition obvious. Teva's expert testified that "stability is an important consideration to a formulator." Smyth Testimony, Trial Tr. 449:16–19. Dr. Smyth agreed that, in light of the skilled artisan's conceded interest in robust, long term stability, "if the person of ordinary skill in the art had wanted to pursue the Kerr formulation, they would have done a similar test and they would have confirmed that those degradants would appear." Smyth Testimony, Trial Tr. 449:16–451:5. The majority's contrary finding is contrary to the record.

The objective indicia of nonobviousness are present: long-felt need, failure of others, unexpected results, copying, commercial success

The panel majority finds a prima facie case of obviousness on finding the separate components of claim 9 in separate references, although there is no teaching or suggestion to make this specific combination. Precedent instructs the decision-maker to place the claimed subject matter in context of the knowledge of persons in the field of the invention, and to this end, to consider objective evidence of the scientific and market realities at the time of the invention.

Evidence of long-felt need, failure of others, unexpected results, commercial success, and copying, help to place a

new discovery in real-world perspective. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) ("[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered. . . [and] may often be 'the most probative and cogent' evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not."). These considerations show how the invention was viewed in the context in which it arose. *See Graham v. John Deere Co.*, 383 U.S. 1 (1966):

> Such inquiries may lend a helping hand to the judiciary which, as Mr. Justice Frankfurter observed, is most ill-fitted to discharge the technological duties cast upon it by patent legislation. *Marconi Wireless Telegraph Co. of America v. United States*, 320 U.S. 1, 60 (1943). They may also serve to "guard against slipping into use of hindsight," *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 ([6th Cir.] 1964), and to resist the temptation to read into the prior art the teachings of the invention in issue.

Id. at 36. The district court applied a flawed analysis, for the objective indicia are properly considered as part of the evaluation of the prima facie case, in determining whether there is clear and convincing evidence of invalidity based on obviousness. *See In re Cyclobenzaprine*, 676 F.3d at 1075 (all of the *Graham* factors must be considered in determining whether there is a prima facie case of obviousness). It is apparent that the district court gave inadequate consideration to the objective evidence of nonobviousness.

Here, the unexpected biological activity of the combination was undisputed, whereby the absorption of naloxone into the bloodstream was increased by 56% compared with the closest prior art, and by a product administered by inhalation instead of needle-injection. The life-saving benefits are conceded. In the absence of any teaching or

suggestion in the prior art to create this method and composition, the evidence of long-felt and unmet need, followed by FDA approval and market success, have weight that must be considered.[4] The FDA's recognition of the need for improved treatment of opioid overdose may well have reinforced the "general motivation" to experiment and search for remedy, but it is not a teaching of the successful invention. *See Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc.*, 933 F.3d 1367 (Fed. Cir. 2019) ("[C]harting a path to the claimed compound by hindsight is not enough to prove obviousness.").

Although the panel majority agrees that the district court erred in its analysis of long-felt need, the majority erroneously accepts the district court's unsupported findings, such as that the skilled artisan would not have been surprised at the efficacy of the product. Maj. Op. 27–29 (citing Dist. Ct. Op. at *44). The district court found that BZK rendered the 56% increase in bioavailability unsurprising, Dist. Ct. Op. at *44, while totally ignoring the prior art teaching that BZK degrades naloxone. There was no contrary evidence. The panel majority seeks to create such evidence from Dr. Smyth's attempts to explain away the prior art.

The majority does not give fair weight to the objective indicia in this area of public concern. It is not disputed that

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[4] The panel majority criticizes the dissent for this position. *See* Maj. Op. 27 n. 12. To the contrary: "[i]t is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included." *In re Cyclobenzaprine*, 676 F.3d at 1075 (quoting *Stratoflex*, 713 F.3d at 1538). *En route* to a conclusion on obviousness, a court must not stop until all pieces of evidence on that issue have been fully considered and each given its appropriate weight. *In re Cyclobenzaprine*, 676 F.3d at 1076.

Narcan® is biologically successful where others had failed. The district court apparently believed that unless FDA approval is "part of the claims," the ability of an invention to achieve FDA approval is irrelevant to determination of non-obviousness. *See* Dist. Ct. Op. at *26. ("Dr. Smyth testified, however, that FDA approval '[was] not part of the claims'" (brackets original)). It is however highly relevant that the FDA stated the need for an effective product "that could be FDA approved." Maj. Op. at 13 (quoting Dist. Ct. Op. at *8). It was undisputed that the invention in the '747 patent succeeded in achieving FDA approval while others failed. *See* Testimony of Dr. Lisbeth Illum, expert for Adapt Pharma, Trial Tr. 733:3–9:

> Q. . . . Now, after the FDA 2012 meeting, were there other companies, aside from the inventors in this case, who tried to make intranasal naloxone products to meet the FDA goal?
>
> A. Yes, there were.
>
> Q. Did any of them arrive at the same combination of features that are claimed in the asserted patents?
>
> A. No.

Dr. Illum discussed the public concerns of opioid overdose, and the need for rapid and effective treatment, as well as the unexpected superiority of Narcan®. *See* Illum testimony, Trial Tr. 764:17–24:

> Q. So there was a 56 percent improvement over Wyse's formulation if you compare the 4-milligrams NARCAN® bioavailability versus the 2-milligram?
>
> A. Yes. . . .
>
> Q. Okay. Was that a -- surprising or not surprising?

A. Oh, it's amazing data if you look at it.

Precedent guides that "the objective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo*, 726 F.3d at 1358. This evidence must receive full and fair consideration. *Graham*, 383 U.S. at 36. The FDA's recognition of the need for improved treatment of opioid overdose may well have reinforced the "general motivation" to search for improvement, but that does not render obvious every successful improvement. This court has previously "consider[ed] the failure of others to obtain FDA approval as relevant objective indicia of nonobviousness." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013).

None of the FDA, the district court, the panel majority, nor the defendant Teva, identified any teaching or suggestion by the FDA (or anyone else) of the Narcan® composition and method. The majority's misapplication of law and precedent will simply become a disincentive to the search for improvements in crowded medicinal fields, lest any success be obvious to the judges. The majority's new standard will deter research in areas in which the FDA has mentioned the need for improvement.

CONCLUSION

The majority's ruling of unpatentability based on obviousness is unsupported by evidence and contrary to law. I respectfully dissent.