

NOTE: This disposition is nonprecedential.

**United States Court of Appeals
for the Federal Circuit**

**ARIUS TWO, INC., BIODELIVERY SCIENCES
INTERNATIONAL, INC.,**
Plaintiffs-Cross-Appellants

v.

**ALVOGEN PB RESEARCH & DEVELOPMENT LLC,
ALVOGEN MALTA OPERATIONS LTD., ALVOGEN,
INC., ALVOGEN GROUP, INC.,**
Defendants-Appellants

2022-1394, 2022-1449

Appeals from the United States District Court for the
District of Delaware in No. 1:18-cv-01395-CFC-CJB, Chief
Judge Colm F. Connolly.

Decided: December 21, 2022

HOWARD W. LEVINE, Dechert LLP, Washington, DC, ar-
gued for plaintiffs-cross-appellants. Also represented by
SHYAM SHANKER, New York, NY; JENNIFER SWAN, Palo
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JEREMY LOWE, Leydig, Voit & Mayer, Ltd., Chicago, IL,
argued for defendants-appellants. Also represented by

DAVID AIRAN, GREGORY BAYS, KEELIN BIELSKI, JAMES
SANNER, STEVEN H. SKLAR, ASHLEE SZELAG.

Before CHEN, CLEVINGER, and CUNNINGHAM, *Circuit
Judges.*

CHEN, *Circuit Judge.*

This Hatch-Waxman case involves an appeal and cross-appeal of the district court’s decision finding some asserted claims of U.S. Pat. Nos. 8,147,866 (’866 patent), 9,655,843 (’843 patent), and 9,901,539 (’539 patent) invalid for obviousness while finding the remaining asserted claims not invalid. With respect to the asserted claims found not invalid, defendants-appellants Alvogen PB Research & Development LLC, Alvogen Malta Operations Ltd., Alvogen, Inc., and Alvogen Group, Inc. (collectively, Alvogen) have not shown the district court erred in making certain evidentiary and procedural findings against Alvogen. Plaintiffs-cross-appellants Arius Two, Inc., and Bidelivery Sciences International, Inc. (collectively, BDSI) have shown that the district court applied an incorrect burden of proof when considering the long-felt need and unexpected results of the asserted claims found invalid for obviousness. We therefore *affirm-in-part, vacate-in-part, and remand.*

BACKGROUND

A

The asserted claims recite methods and devices for administering buprenorphine, an opioid, using a bi-layer film placed inside a patient’s cheek. *See, e.g.,* ’866 patent col. 3 ll. 6–31. The bi-layer film includes a bioerodable mucoadhesive (BEMA) layer containing buprenorphine and a backing layer located between the BEMA layer and the oral cavity. *Id.* at Fig. 4A–4C and col. 3 ll. 25–31. The district court found that after placement inside the cheek of a

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patient, the BEMA layer adheres to the cheek's surface and is dissolved by saliva, allowing the buprenorphine to permeate into the cheek's tissue where it enters the blood. *Biodelivery Scis. Int'l, Inc. v. Alvogen PB Rsch. & Dev. LLC*, 576 F. Supp. 3d 184, 191-92 (D. Del. 2021) (*Opinion*). As the BEMA layer dissolves, the backing layer prevents the buprenorphine from entering the oral cavity and being ingested. *Id.*

BDSI sued Alvogen after Alvogen submitted an Abbreviated New Drug Application to FDA for approval to market a generic version of BDSI's Belbuca® drug product. *Id.* at 189. BDSI asserted the following claims against Alvogen at trial:

- Claims 4 and 5 of the '866 patent (the Pharmacokinetic Claims), which claim pharmacokinetic properties;
- Claims 9 and 20 of the '539 patent (the pH of the Backing Layer Claims), which claim both a certain pH of the BEMA layer and a certain pH of the backing layer; and
- Claims 3 and 10 of the '866 patent; and claims 8, 9, and 20 of the '843 patent (the pH of the BEMA Layer Claims), which claim a certain pH of the BEMA layer.

Id. at 189–90.

B

After a bench trial, the district court found that the Pharmacokinetic Claims were not invalid, the pH of the Backing Layer Claims were not invalid, and the pH of the BEMA Layer Claims were invalid as obvious.

As part of its obviousness findings, the district court determined that a skilled artisan would have known buprenorphine exhibits a high first-pass effect. *Id.* at 200. This means when buprenorphine is ingested, the liver

breaks down the compound into less effective chemicals, thereby greatly decreasing the drug's bioavailability because less buprenorphine reaches the blood plasma. *Id.* at 196. The district court also considered a prior art reference teaching an adhesive bi-layer film to administer a variety of drugs, including opioids, producing "excellent bioavailability, fast onset, and sustained delivery." *Id.* at 197–98, 200 (citing J.A. 60929 at [0131]). The district court also found a skilled artisan would have considered both the solubility and absorption rate of buprenorphine into the mucosal membrane in order to maximize bioavailability (as measured by the portion of the drug that reaches the blood plasma). *Id.* at 201; *see also id.* at 196. Specifically, the district court found that a skilled artisan would have recognized buffering a buprenorphine solution to a pH range between about 4 and 6 would likely maximize bioavailability by providing good solubility and absorption. *Id.* at 201–02.

The district court held the Pharmacokinetic Claims not invalid because Alvogen failed to show a skilled artisan would have been motivated to combine the prior art references and waived its inherency argument by failing to raise the argument in the pre-trial order. *Id.* at 202–03 n.4, 203. The district court also held the pH of the Backing Layer Claims not invalid because Alvogen failed to show the pH of the backing layer was inherently present in the prior art and because secondary considerations supported a finding of nonobviousness. *Id.* at 209. However, the district court held the pH of the BEMA Layer Claims invalid as obvious because a skilled artisan would have been motivated to combine certain prior art references with a reasonable expectation of success to arrive at the claimed invention. *Id.* at 200–02, 206. With respect to the pH of the BEMA Layer Claims, the district court also stated BDSI had not: (1) "clearly and convincingly" shown evidence of a long-felt need, (2) shown the prior art taught away, or (3) shown unexpected results. *Id.* at 203–05.

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Alvogen timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal, Alvogen argues the district court clearly erred as to certain findings it made in holding the Pharmacokinetic Claims and the pH of the Backing Layer Claims not invalid. On cross-appeal, BDSI argues that the district court applied the incorrect legal standard when considering secondary considerations of nonobviousness regarding the pH of the BEMA Layer Claims.

Obviousness is a mixed question of law and fact. We review the district court's legal conclusions regarding obviousness de novo and any factual findings for clear error. *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017). Whether a skilled artisan would be motivated to combine prior art references to find obviousness and whether secondary considerations support a finding of nonobviousness are factual issues. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1327 (Fed. Cir. 2017). A factual finding is clearly erroneous only if “despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made.” *Merck*, 874 F.3d at 728.

I. Pharmacokinetic Claims

Alvogen argues the district court clearly erred in finding that a skilled artisan would not have been motivated to combine three references¹ with a reasonable expectation of

¹ R.E.S. Bullingham, et al., *Sublingual Buprenorphine Used Postoperatively: Clinical Observation and Preliminary Pharmacokinetic Analysis*, 12 *British J. Clinical Pharmacology* 117 (1981) (Bullingham I); U.S. Pat. App. Pub. No. 2005/0147658 (Tapolsky); and European Pat. App. Pub. No. 0069600 (Todd).

success to arrive at the Pharmacokinetic Claims. *See, e.g.*, Appellants' Br. 37. Alvogen concedes, however, that it did not clearly articulate in its post-trial briefing that a skilled artisan would have been motivated to combine the references to arrive at the Pharmacokinetic Claims. Oral Arg. 39:51–41:18. Based on the record before us, we do not discern any clear error made by the district court in finding no motivation to combine the asserted prior art references to arrive at the Pharmacokinetic Claims. *See Stryker Corp. v. Intermedics Orthopedics, Inc.*, 96 F.3d 1409, 1415 (Fed. Cir. 1996).

Alvogen also argues the Pharmacokinetic Claims would have been obvious because they simply state an inherent property of the otherwise obvious BEMA Layer Claims. Appellants' Br. 45–46. The district court found Alvogen waived this argument by failing to raise it before trial. *Opinion* at 202–03 n.4; Order Granting Motion to Strike, *BioDelivery Scis. Int'l, Inc. v. Alvogen PB Rsch. & Dev. LLC*, No. 1:18-cv-01395, ECF No. 281 (D. Del. Sept. 21, 2021) (granting BDSI's motion to strike certain inherency arguments from Alvogen's post-trial briefing). Alvogen argues here, as it did at the district court, that its citation of cases generally discussing inherency in its pre-trial order avoids waiver. Appellants' Reply Br. 49–50. However, Alvogen has not shown where in the pre-trial order it actually raises any argument with respect to the inherency of the Pharmacokinetic Claims. Accordingly, the district court did not err in finding Alvogen's inherency argument waived.²

² Contrary to Alvogen's argument that the district court's footnote 4 suggests Alvogen did not waive all possible inherency arguments (Appellants' Reply Br. 49), footnote 4, when read in light of the district court's order granting BDSI's motion to strike Alvogen's inherency

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We affirm the district court's conclusion that the Pharmacokinetic Claims are not invalid.

II. pH of the Backing Layer Claims

Alvogen argues that the district court erred in finding the pH of the Backing Layer Claims not invalid because Alvogen showed that the claimed backing layer pH was inherent in the prior art. *See, e.g.*, Appellants' Br. 54. Alvogen explains its expert testified, and BDSI did not dispute, that the pH of the backing layer of Belbuca[®] was between 4.5 and 4.7. Alvogen's expert further testified that Belbuca[®] and the prior art formulation have "identical ingredients present in materially identical amounts," and because the formulations are nearly the same, one would expect both formulations to have the same pH, i.e., a pH between 4.5 and 4.7. Appellants' Br. 58–60. Thus, Alvogen argues the prior art inherently includes the claimed pH range of the backing layer in the '539 patent (between about 4.0 and about 4.8). *Id.*

In response, BDSI highlights an inventor declaration submitted during the prosecution of the '539 patent reciting results showing—on average—the pH of the backing layer of the prior art was 5.61, which is outside the '539 patent's claimed range. Cross-Appellants' Br. 52 (citing J.A. 69125).

As a preliminary matter, Alvogen contends the district court abused its discretion by considering the inventor declaration as evidence because it is hearsay. Appellants' Reply Br. 2–4, 61. BDSI responds that the district court properly considered the declaration because Alvogen entered it into evidence as an admission of a party opponent without limiting the purpose for which the declaration could be used and questioned its own expert regarding the

argument, is properly understood as finding Alvogen's inherency argument waived.

declaration's content. Cross-Appellants' Br. 53–54. Because the inventor declaration was introduced by Alvogen without any limitation on its use, we find that the district court did not err by considering the inventor declaration for all that it discloses. See *Ohler v. United States*, 529 U.S. 753, 755 (2000) (explaining that “a party introducing evidence cannot complain on appeal that the evidence was erroneously admitted”).

Regarding the district court's finding that Alvogen did not show the pH of the backing layer to be inherent in the prior art, we find no clear error in the district court's reasoning. The district court weighed Alvogen's expert's testimony with BDSI's inventor declaration and found that “the incompatible representations in the record” indicated Alvogen had not proven with clear and convincing evidence that the prior art taught a backing layer with the claimed pH. *Opinion*, 576 F. Supp. 3d at 208–09. The district court also found the only evidence offered by Alvogen to rebut the credibility of the inventor declaration was testimony from Alvogen's expert stating the pH measured in the declaration “didn't make sense.” *Id.* at 209 n.7. The district court also found changing the backing layer pH unexpectedly affected the bioavailability of buprenorphine—a lower backing layer pH resulted in increased bioavailability. *Id.* at 209. We find no clear error in the district court's findings and therefore affirm the district court's decision holding the pH of the Backing Layer Claims not invalid.

III. pH of the BEMA Layer Claims

BDSI, on cross-appeal, argues the district court wrongly applied the clear and convincing standard when analyzing certain secondary considerations of nonobviousness—i.e., the long-felt need and unexpected results of the

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pH of the BEMA Layer Claims.³ Alvogen contends the district court applied the correct standard and that any language in the *Opinion* indicating otherwise was inadvertent.

A

The *Opinion* correctly states that the patent challenger must prove obviousness by clear and convincing evidence, *id.* at 194, and that a fact finder must consider secondary considerations of nonobviousness before reaching an obviousness conclusion, *id.* at 193–94 (citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012)). Secondary considerations must be established by a preponderance of the evidence. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc).

The *Opinion* does not explicitly identify a burden of proof by which the patent owner must prove secondary considerations. The *Opinion* did find, however, that BDSI failed “to show *clearly and convincingly* that Belbuca® answered a long felt, but unresolved need in medicine.” *Opinion*, 576 F. Supp. 3d at 203 (emphasis added). BDSI argues this statement shows the district court applied the wrong

³ BDSI also argues on appeal that the district court erred in its motivation to combine with a reasonable expectation of success analysis because even if a skilled artisan would have expected *some* increase in bioavailability after decreasing the pH of the BEMA layer, a skilled artisan would not have expected an increase to the degree obtained. Cross-Appellants’ Br. 69. We do not find this argument in BDSI’s post-trial briefing and therefore do not consider it on appeal. *See MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1271 (Fed. Cir. 2013) (explaining that a theory not ultimately raised at a bench trial is waived).

standard in assessing long-felt need. Cross-Appellants' Br. 65–66. Alvogen argues that the district court's word choice was inadvertent error, and regardless of the exact language used, the district court's extensive analysis of the evidence presented and recognition that secondary considerations must be considered show the district court applied the correct standard. Appellants' Reply Br. 21.

Based on our review, the fairest reading of the *Opinion* is that it incorrectly required BDSI to prove long-felt need by clear and convincing evidence. We cannot say this is harmless error. While it is true the district court never explicitly stated it applied the heightened “clear and convincing” standard to BDSI's evidence of secondary considerations, the district court did not state the proper standard either. Nor could we identify the correct standard being clearly stated for the district court in the parties' pre-trial order. Furthermore, the *Opinion*'s analysis used the language of the heightened “clear[] and convincing[]” standard, and Alvogen has not persuasively shown that this was inadvertent. Although the district court thoroughly analyzed the evidence presented at trial, the district court's thorough analysis and recognition that secondary considerations must be considered do not indicate that it would have reached the same conclusion regarding BDSI's long-felt need evidence based on a more lenient standard. Therefore, we find the district court applied an incorrect standard in considering the long-felt need of the pH of the BEMA Layer Claims.

B

BDSI also argues the district court applied the same incorrect heightened evidentiary standard to its analysis of unexpected results, and under the correct standard, the district court should have found evidence of unexpected results. Cross-Appellants' Br. 66–69. Instead of arguing that the district court did not apply a heightened standard, Alvogen responds to BDSI's substantive arguments

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regarding the district court's findings of unexpected results. Appellants' Reply Br. 25–30. Alvogen's arguments here are no more persuasive than its arguments with respect to long-felt need. For the same reasons as discussed above, we find the district court did not apply the proper standard in considering the unexpected results of the inventions covered by the pH of the BEMA Layer Claims.

Because the district court should have considered the secondary considerations evidence presented to it under the preponderance of the evidence standard, we vacate the district court's judgment regarding obviousness of the pH of the BEMA Layer Claims and remand.⁴

CONCLUSION

We have considered both Alvogen and BDSI's remaining arguments and do not find them persuasive. For the foregoing reasons:

- We affirm the district court's finding that the Pharmacokinetic Claims (claims 4 and 5 of the '866 patent) and the pH of the Backing Layer Claims (claims 9 and 20 of the '539 patent) are not invalid; and
- We vacate the district court's judgment that the pH of the BEMA Layer Claims (claims 3 and 10 of the '866 patent; and claims 8, 9, and 20 of the '843 Patent) are invalid as obvious and remand for the sole

⁴ Our decision to remand is not an invitation for either party to introduce additional evidence into the record. We only ask the district court to re-evaluate the evidence already presented at trial to determine whether the evidence—although not sufficient to meet the clear and convincing standard—is sufficient to meet the preponderance of the evidence standard.

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purpose of reconsidering the evidence already presented at trial regarding long-felt need and unexpected results under the correct evidentiary standard.

**AFFIRMED IN PART, VACATED IN PART, AND
REMANDED**

COSTS

No costs.