

NOTE: This disposition is nonprecedential.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
Alto, CA.

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).

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