United States Court of Appeals for the Federal Circuit

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,
Plaintiffs-Appellants

v.

NORWICH PHARMACEUTICALS INC.,
Defendant-Cross-Appellant

2022-2153, 2023-1952

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Judge Richard G. Andrews.

Decided: April 11, 2024

WILLIAM R. PETERSON, Morgan, Lewis & Bockius LLP, Houston, TX, argued for plaintiffs-appellants. Also represented by MICHAEL J. ABERNATHY, KARON NICOLE FOWLER, MICHAEL SIKORA, Chicago, IL; JULIE S. GOLDEMBERG, Philadelphia, PA; JOSHUA DANIEL CALABRO, SHANNON KEOUGH CLARK, STEVEN C. KLINE, ALEXIS M. MCJOYNT, SCOTT K. REED, BECKY E. STEEPHENSON, Venable LLP, New York, NY.

CHAD A. LANDMON, Axinn, Veltrop & Harkrider LLP,

Hartford, CT, argued for defendant-cross-appellant. Also represented by MATTHEW BECKER, REBECCA L. CLEGG, THOMAS K. HEDEMANN, MATTHEW S. MURPHY.

IRENA ROYZMAN, Kramer Levin Naftalis & Frankel LLP, New York, NY, for amici curiae Regeneron Pharmaceuticals, Inc., Ocular Therapeutix, Inc. Also represented by CHRISTINE WILLGOOS; PAUL BRZYSKI, Washington, DC.

PAUL WHITFIELD HUGHES, III, McDermott Will & Emery LLP, Washington, DC, for amicus curiae Vanda Pharmaceuticals Inc. Also represented by CHRISTOPHER MICHAEL BRUNO, SARAH HOGARTH, APRIL ELISE WEISBRUCH.

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

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

Opinion dissenting-in-part filed by *Circuit Judge* CUNNINGHAM.

LOURIE, *Circuit Judge*.

Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.P.A. (collectively, "Salix") appeal from a final judgment of the United States District Court for the District of Delaware holding claim 2 of U.S. Patent 8,309,569, claim 3 of U.S. Patent 10,765,667, claim 4 of U.S. Patent 7,612,199, and claim 36 of U.S. Patent 7,902,206 invalid as obvious. *See Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-cv-430, 2022 WL 3225381 (D. Del. Aug. 10, 2022) ("*Decision*").

Norwich Pharmaceuticals Inc. ("Norwich") cross-appeals from an order that issued after the district court concluded that Norwich infringed claim 8 of U.S. Patent 8,624,573, claim 6 of U.S. Patent 9,421,195, and claims 11 and 12 of U.S. Patent 10,335,397 and had failed to prove

that those claims were invalid. That order, contained within the final judgment, instructed the FDA that the effective approval date of Norwich's Abbreviated New Drug Application ("ANDA") may not precede the expiration dates of those claims. J.A. 51. Norwich also cross-appeals from a denial of its motion to modify the final judgment. *See Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-430, 2023 WL 3496373 (D. Del. May 17, 2023) ("*Rule 60(b) Order*").

For the following reasons, we affirm.

BACKGROUND

Rifaximin, the active ingredient in Salix's commercial product Xifaxan®, has been widely used as an antibiotic for decades, having been first synthesized in the early 1980s in Italy and approved there as an antibiotic in 1985. *Decision* at *8; J.A. 2532. The FDA approved Xifaxan nearly 20 years later, in 2004, as 200 mg tablets for the treatment of travelers' diarrhea. *Decision* at *1. The FDA subsequently approved 550 mg tablets for hepatic encephalopathy ("HE") in 2010 and for irritable bowel syndrome with diarrhea ("IBS-D") in 2015. *Id.*

Norwich sought to market a generic version of rifaximin and, in 2019, filed an ANDA for 550 mg tablets with the same indications as Xifaxan, certifying pursuant to 21 U.S.C. § 355(j)(2)(vii)(IV) that Salix's rifaximin patents were invalid. Salix timely sued, asserting that Norwich's ANDA infringed dozens of valid, Orange Book-listed patents. By the time of trial, the case had been streamlined to three groups of patents:

- the '573, '195, and '397 patents, directed to treating HE ("the HE patents");
- the '569 and '667 patents, directed to treating IBS-D with 550 mg rifaximin three times a day (1,650 mg/day) for 14 days ("the IBS-D patents"); and,

- the '199 and '206 patents, directed to rifaximin form ß ("the polymorph patents").

Following a bench trial, the district court held that Norwich infringed the HE patents' claims and had failed to establish their invalidity. *Decision* at *10–11. Norwich did not appeal those holdings. The court also held that Norwich's ANDA infringed the IBS-D and polymorph patents, but that those patents' claims would have been obvious over certain prior art. *Id.* at *2–3, 16–17. Salix appealed those invalidity holdings.

As part of the entered judgment, the district court ordered that the effective date of a final approval of Norwich's ANDA should not precede October 2029, which is the latest expiration date associated with the HE patents. J.A. 51. Norwich then amended its ANDA in an attempt to remove the infringing HE indication and moved to modify the judgment under Federal Rule of Civil Procedure 60(b), asserting that the amendment negated any possible infringement. The court denied Norwich's motion, and Norwich cross-appealed.

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

DISCUSSION

Salix first contends that the district court's conclusion that the asserted claims of the IBS-D patents were invalid as obvious was reached in error. Subsumed within that challenge is a question of whether or not a background reference discussed by the court was properly established as prior art. Salix also contends that the court erred in holding that the asserted polymorph patent claims were invalid as obvious. Norwich's cross-appeal asserts that the court erred in the phrasing of its order precluding final approval of its ANDA until expiration of the HE patents. Norwich further asserts that the court erred in denying its motion to modify after the ANDA was amended in an attempt to avoid infringement. We address each argument in turn.

I

We turn first to Salix's contention that the district court erred in concluding that the asserted claims of the IBS-D patents would have been obvious over the asserted prior art.

Whether or not a claim would have been obvious is a question of law, based on underlying factual determinations. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1328–29 (Fed. Cir. 2020). We review the ultimate legal question of obviousness *de novo* and the underlying factual determinations for clear error. *Id.* at 1328. A finding is clearly erroneous only if we are "left with a definite and firm conviction that the district court was in error." *Id.* (citations omitted).

The IBS-D patents are directed to treating IBS-D with 550 mg rifaximin, thrice-daily (1,650 mg/day), for 14 days. For example, claim 2 of the '569 patent depends from claim 1 as follows:

> 1. A method of providing acute treatment for diarrhea-associated Irritable Bowel Syndrome (dIBS) comprising: *administering 1650 mg/day* of rifaximin for 14 days to a subject in need thereof, wherein removing the subject from treatment after the 14 days results in a durability of response, wherein the durability of response comprises about 12 weeks of adequate relief of symptoms.
>
> 2. The method of claim 1, wherein *the 1650 mg is administered at 550 mg three times per day*.

'569 patent, col. 30 ll. 4–12 (emphases added); *see also* '667 patent, col. 46 ll. 29–33, 39–40 (claims 1 & 3, similar). The key limitation on appeal is the dosage amount that appears in the claims: 550 mg, three times per day ("TID"), for a total of 1,650 mg/day.

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