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.

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