United States Court of Appeals for the Federal Circuit

YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Appellant

v.

MYLAN PHARMACEUTICALS INC., AMNEAL PHARMACEUTICALS LLC,
Appellees

2017-1594, 2017-1595, 2017-1596

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2015-00643, IPR2015-00644, IPR2015-00830, IPR2015-01976, IPR2015-01980, IPR2015-01981.

Decided: October 12, 2018

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for appellant. Also represented by WILLIAM G. JAMES, II; ELIZABETH HOLLAND, New York, NY; DARYL L. WIESEN, Boston, MA; JOHN C. O'QUINN, Kirkland & Ellis LLP, Washington, DC; LESLIE M. SCHMIDT, New York, NY.

DAVID LEE ANSTAETT, Perkins Coie, LLP, Madison, WI, argued for appellees. Appellee Mylan Pharmaceuticals Inc. also represented by SHANNON BLOODWORTH, ROBERT SWANSON, BRANDON MICHAEL WHITE, Washington, DC; DAN L. BAGATELL, Hanover, NH; CHRISTINA JORDAN MCCULLOUGH, Seattle, WA.

ANTHONY JAMES FITZPATRICK, Duane Morris LLP, Boston, MA, for appellee Amneal Pharmaceuticals LLC. Also represented by VINCENT CAPUANO, CHRISTOPHER S. KROON; PATRICK GALLAGHER, Boca Raton, FL.

Before REYNA, BRYSON, and STOLL, *Circuit Judges*.

REYNA, *Circuit Judge*.

In this consolidated appeal, Appellant Yeda Research & Development Co., Ltd. challenges the Patent Trial and Appeal Board's final written decisions finding the claims of U.S. Patent Nos. 8,232,250, 8,399,413, and 8,969,302 unpatentable as obvious in three *inter partes* review proceedings. We affirm the Board's decisions.[1]

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[1] In a companion case decided today, *Teva Pharmaceuticals USA, Inc. v. Sandoz Inc.*, No. 17-1575 (Fed. Cir. Oct. 12, 2018), Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co., Ltd., appeal the decision of the United States District Court for the District of Delaware invalidating all asserted claims of U.S. Patent Nos. 8,232,250, 8,399,413, 8,969,302, and 9,155,776.

BACKGROUND

I. Patents at Issue

Yeda Research and Development Co., Ltd. ("Yeda") is the assignee of U.S. Patents Nos. 8,232,250, 8,399,413, and 8,969,302 (the '250, '413, and '302 patents, respectively), all entitled "Low Frequency Glatiramer Acetate Therapy." The patents, collectively referred to as the "Copaxone patents," share a common specification and claim priority to the same two provisional applications. *See* J.A. 267, 279, 291. The earliest priority date of the Copaxone patents is August 20, 2009. *Id.*

The Copaxone patents describe and claim COPAXONE® 40mg/mL, a treatment for relapsing-remitting multiple sclerosis ("RRMS"). RRMS is a form of multiple sclerosis, an autoimmune disorder that causes the body's immune system to attack the central nervous system. RRMS is characterized by unpredictable relapses followed by periods of remission with no new signs of disease activity.

The active ingredient in COPAXONE® 40mg/mL is glatiramer acetate ("GA"), a synthetic mixture of polypeptides. GA is also known as "copolymer 1" or "Cop. 1." COPAXONE® 40mg/mL is supplied as a single-dose prefilled syringe. Broadly, the treatment consists of the injection of 40mg of GA three times a week, abbreviated "40mg GA 3x/week." Relevant to this appeal, side effects of GA injections include injection-site reactions ("ISRs") and immediate post-injection reactions ("IPIRs"). ISRs are physical symptoms at the injection site, such as swelling or itchiness. IPIRs are reactions immediately following an injection, such as flushes, sweating, or palpitations.

Prior to COPAXONE® 40mg/mL, in 1996 the Food and Drug Administration ("FDA") approved

COPAXONE® 20mg/mL, a regimen consisting of the daily injection of 20mg GA. Daily GA injections were known to subject patients to discomfort, including side effects in the form of ISRs and IPIRs. J.A. 6956.

For analyzing the obviousness of the Copaxone patents, a key limitation of the claims is the administration of a 40mg GA dose in three subcutaneous injections over seven days. Claim 1 of the '250 patent is representative:

> 1. A method of alleviating a symptom of relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis comprising administering to the human patient a therapeutically effective regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient to alleviate the symptom of the patient.

'250 patent col. 16 ll. 35–45.

Certain claims of the '250 and '413 patents further require improved tolerability and/or reduced frequency of injection reactions in the claimed regimen as compared to 20mg daily. '250 patent col. 17 l. 24–col. 18 l. 6; '413 patent col. 16 ll. 51–54.

Apart from claim 1 of the '302 patent, all independent claims require at least one day between doses. '250 patent col. 16 ll. 35–45, col. 17 l. 25–col. 18 l. 6, col. 18 ll. 19–26; '413 patent col. 16 ll. 26–36, col. 18 ll. 1–13, col. 18 ll. 14–28; '302 patent col. 17 ll. 4–12. Claim 1 of the '302 patent does not specify any

particular interval between doses, but dependent claims 4 and 5 limit injections to certain combinations of days of the week, all with at least one day between injections, and independent claim 10 of the '302 patent requires that the injection be administered "three times per week with at least one day between every subcutaneous injection." '302 patent col. 16 ll. 37–41, col. 16 ll. 47–58, col. 17 ll. 4–12.

II. Prior Art References

The first clinical trial for using GA to treat multiple sclerosis was in 1987 by Dr. Bornstein et al. ("Bornstein"),[2] which was followed later by a Teva Phase III clinical trial in 1995. Both Bornstein and the Phase III trial tested 20mg GA daily. J.A. 7279–80, 7282–85, 6895–7235. The 20mg/day dose was selected without performing conventional optimal-dose-finding studies. J.A. 7239.

The Bornstein study showed that GA administered subcutaneously for two years at a daily dose of 20mg "produced clinically important and statistically significant beneficial effects." J.A. 7284. Participants in both Bornstein and the Phase III trial reported ISRs and IPIRs as side effects. J.A. 7284, 6934. The Phase III trial noted "adverse experience" as the main reason contributing to patient dropout, and "[t]he most common adverse event associated with dropout was injection site reaction." J.A. 6934. A Phase III trial reviewer made recommendations for future researchers to explore dose-response and dose-ranging studies, asking "Is 20 mg the optimum dose? Are daily injections necessary?" J.A. 6956.

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[2] Murray B. Bornstein et al., *A Pilot Trial of COP 1 in Exacerbating-Remitting Multiple Sclerosis*, 317 New Eng. J. Med. 408, 408–14 (1987).

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