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Paper 54
Entered: February 7, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KOIOS PHARMACEUTICALS LLC,
Petitioner,

v.

MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH,
Patent Owner.

Case IPR2016-01370
Patent 8,664,231 B2

Before JACQUELINE WRIGHT BONILLA, *Vice Chief Administrative Patent Judge*, TONI R. SCHEINER, and ERICA A. FRANKLIN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Koios Pharmaceuticals LLC ("Petitioner") filed a Petition on July 20, 2016, requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,664,231 B2 (Ex. 1001, "the '231 patent"). Paper 1 ("Pet."). Petitioner provided the Declarations of Donald R. Miller, Pharm.D (Ex. 1033), and Michael H. Schiff, M.D. (Ex. 1034), in support of its positions. medac Gesellschaft für klinische Spezialpräparate mbH ("Patent Owner") filed a Preliminary Response on November 10, 2016. Paper 11 ("Prelim. Resp.").

We instituted *inter partes* review on February 8, 2017 as to claims 1–22. Paper 13 ("Institution Decision" or "Inst. Dec."). Specifically, we instituted *inter partes* review on the following grounds:

Reference(s)	**Basis**	**Claim(s)**
Grint[1]	§ 102(b)[2]	1, 2, 4–6, 11–13, 17, and 22
Grint, Arthur,[3] Moitra,[4] and Insulin Admin.[5]	§ 103(a)	7–10, 14–16, and 19–21

[1] U.S. Patent No. 6,544,504 B1, issued April 8, 2003 (Ex. 1003, "Grint").

[2] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the '231 patent has an effective filing date before March 16, 2013, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

[3] Valerie Arthur et al., *A Study of Parenteral Use of Methotrexate in Rheumatic Conditions*, 11 J. CLINICAL NURSING 256 (2002) (Ex. 1023, "Arthur").

[4] R.K. Moitra et al., *Caveats to the Use of Parenteral Methotrexate in the Treatment of Rheumatic Disease*, 44 RHEUMATOLOGY 256 (2005) (Ex. 1025, "Moitra").

[5] Am. Diabetes Ass'n, *Insulin Administration*, 26 DIABETES CARE S121 (Supp. 1 2003) (Ex. 1015, "Insulin Admin.").

Reference(s)	Basis	Claim(s)
Grint and Alsufyani[6]	§ 103(a)	18
Wyeth[7]	§ 102(b)	1–6, 11–13, 17, 18, and 22
Wyeth, Brooks,[8] Arthur, and Moitra	§ 103(a)	1–6, 11–13, 17, 18, and 22

Inst. Dec. 37.

Patent Owner filed a Patent Owner Response (Paper 24, "PO Resp."), and provided the Declarations of Elena M. Massarotti, M.D. (Ex. 2018), Sean Nicholson, Ph.D. (Ex. 2032), Thomas M. Zizic, M.D. (Ex. 2092), and John S. Clark, Pharm.D. (Ex. 2093) in support of its positions. Petitioner filed a Reply (Paper 37, "Reply"), and Patent Owner filed a Surreply (Paper 43, "Surreply"). We granted Patent Owner's request to file the Surreply to allow Patent Owner to cite to additional portions of Dr. Zizic's deposition testimony intended to provide the full context of portions of Dr. Zizic's deposition testimony cited by Petitioner in the Reply. Paper 42, 2–3.

Additionally, Patent Owner filed a Motion to Exclude Evidence (Paper 39, "Motion to Exclude" or "Mot. to Exclude"), Petitioner filed a

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[6] Khayriah Alsufyani et al., *The Role of Subcutaneous Administration of Methotrexate in Children with Juvenile Idiopathic Arthritis Who Have Failed Oral Methotrexate*, 31 J. RHEUMATOLOGY 179 (2004) (Ex. 1006, "Alsufyani").

[7] Wyeth Pharmaceuticals, Methotrexate Sodium for Injection (2004) (Ex. 1021, "Wyeth").

[8] Paul J. Brooks et al., *Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients with Rheumatoid Arthritis*, 33 ARTHRITIS & RHEUMATISM 91 (1990) (Ex. 1008, "Brooks").

Response to the Motion to Exclude (Paper 46), and Patent Owner filed a Reply in support of the Motion to Exclude (Paper 49).

We heard oral argument on November 7, 2017. A transcript of the argument has been entered into the record. Paper 53 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). For the reasons that follow, we determine that Petitioner has not proven by a preponderance of the evidence that claims 1–22 are unpatentable. Patent Owner's Motion to Exclude Evidence is dismissed as moot.

A. Related Proceedings

Petitioner and Patent Owner identify a district court action involving the '231 patent, titled *medac Pharma, Inc. v. Antares Pharma, Inc.*, No. 1:14-cv-1498-JBS-KMW (D.N.J.). Pet. 2; Paper 4, 2. The parties also identify two prior proceedings at the Board, IPR2014-01091 ("the -1091 IPR") and IPR2016-00649 ("the -649 IPR"), as well as Decisions on Institution in each of those cases, addressing challenges of the same patent and claims at issue here. Pet. 2–3; Paper 12, 3; *Frontier Therapeutics, LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2016-00649 (PTAB Sept. 1, 2016) (Paper 10); *Antares Pharma, Inc. v. medac Gesellschaft für klinische Spezialpräparate mbH*, Case IPR2014-01091 (PTAB Jan. 6, 2015) (Paper 7). The district court litigation settled in April 2015. Paper 4, 2. The -1091 IPR and -649 IPR proceedings were terminated in view of settlements in April 2015 and December 2016, respectively. Pet. 3; Paper 12, 3.

Patent Owner also identifies U.S. Patent Application Serial No. 14/635,542 ("the '542 application"), filed March 2, 2015 (now abandoned). Paper 4, 2.

B. The '231 Patent

The '231 patent relates to a method for treating inflammatory autoimmune diseases, such as rheumatoid arthritis, juvenile arthritis, and psoriasis, by subcutaneously administering a concentrated methotrexate solution comprising more than 30 mg/ml of methotrexate. Ex. 1001, Abstract, 3:59–67, 8:43–47. Methotrexate is a cytostatic agent that has been known since the early 1950s in the field of oncology, particularly for treating leukemia in children and breast cancer. *Id.* at 1:14–17, 1:24–27. Methotrexate also was used to treat psoriasis, and first observed in the late 1950s as a treatment for individual rheumatoid arthritis cases. *Id.* at 1:28–32.

According to the '231 patent, "[o]ver the years, methotrexate has become the gold standard in the treatment of rheumatoid arthritis." *Id.* at 2:34–36. As a basic therapeutic for rheumatoid arthritis, methotrexate is administered orally or parenterally, once a week, over a long period of time, sometimes throughout the patient's lifetime. *Id.* at 2:37–41. Methotrexate is dosed significantly lower in the treatment of rheumatoid arthritis than in the treatment of tumors, sometimes up to 1,000 times lower. *Id.* at 1:56–59. Anti-rheumatic therapy is therefore referred to as "low-dosage methotrexate therapy." *Id.* at 1:59–60. In this capacity, methotrexate is administered only once per week, in dosages ranging from 5–30 mg per week in Germany, and up to 40 mg per week in other European countries. *Id.* at 1:60–65.

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