Trials@uspto.gov
571.272.7822

Paper No. 13
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
APOTEX INC., APOTEX CORP.,
TEVA PHARMACEUTICALS USA, INC.,
FRESENIUS KABI USA, LLC, and WOCKHARDT BIO AG,
Petitioner,

v.

ELI LILLY & COMPANY,
Patent Owner.

Case IPR2016-00237[1]
Patent 7,772,209 B2

Before JACQUELINE WRIGHT BONILLA, MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judges*, and LORA M. GREEN, *Administrative Patent Judge*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining That Claims 1–22 Have Not Been Shown to Be Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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[1] Cases IPR2016-01190, IPR2016-01335, and IPR2016-01341 have been joined with the instant proceeding.

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I. INTRODUCTION

Neptune Generics, LLC, filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 7,772,209 B2 (Ex. 1001, "the '209 patent"). Paper 1 ("Pet."). Eli Lilly & Company ("Patent Owner" or "Lilly") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–22 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on June 3, 2016, as to all of the challenged claims of the '209 patent. Paper 13 ("Institution Decision" or "Dec. Inst.").

Thereafter, other parties filed three additional Petitions challenging the same claims based on the same ground of unpatentability over the same prior art as those instituted by the Board in the instant case, as well as motions for joinder. Specifically, Apotex Inc. and Apotex Corp. requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01190, and joinder to the instant proceeding. IPR2016-01190, Papers 2 and 3. On October 6, 2016, the Board instituted *inter partes* review in that case and granted joinder. IPR2016-01190, Paper 11. Wockhardt Bio AG also requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01335, as well as joinder to the instant proceeding. IPR2016-01335, Papers 1 and 3. *Inter partes* review was instituted in that case and joinder granted on November 18, 2016. IPR2016-01335, Paper 8. Finally, Teva Pharmaceuticals USA, Inc., and Fresenius Kabi USA, LLC, also requested *inter partes* review of claims 1–22 of the '209 patent in IPR2016-01341, and joinder to the instant proceeding. IPR2016-01341, Papers 2 and 3. *Inter*

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partes review was instituted and joinder granted on October 6, 2016. IPR2016-01341, Paper 10. We collectively refer to all enjoined Petitioners in this Final Written Decision as "Petitioner."

Patent Owner filed a Response (Paper 33, "PO Resp."), Petitioner filed a Reply (Paper 48), and Patent Owner filed a Sur-reply (Paper 63). Petitioner filed a Motion to Exclude (Paper 57, "Mot. Exclude"), to which Patent Owner filed an Opposition (Paper 67, "Opp. Mot. Exclude"), and Petitioner filed a Reply (Paper 74). Oral hearing was held on March 16, 2017, and a transcript of that hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). 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). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Based on the record before us, we conclude that Petitioner has failed to demonstrate by a preponderance of the evidence that claims 1–22 of the '209 patent are unpatentable. We also *deny* Petitioner's Motion to Exclude.

A. Related Proceedings

The '209 patent is the subject of litigation in the U.S. District Court for the Southern District of Indiana, including *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, No. 1:10-cv-1376 (S.D. Ind.) (filed Oct. 29, 2010). Pet. 2–3; Prelim. Resp. 2.

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The ’209 patent also has been challenged in IPR2016-00240 by Neptune Generics, LLC, and in IPR2016-00318 by Sandoz Inc. Proceedings IPR2016-01191, IPR2016-01337, and IPR2016-01343 have been joined with IPR2016-00240, and proceedings IPR2016-01393, IPR2016-01340, and IPR2016-01429 have been joined with IPR2016-00318.

B. The ’209 Patent

The ’209 patent issued on August 10, 2010, listing Clet Niyikiza as the sole inventor. Ex. 1001. The ’209 patent claims priority to a series of applications, the earliest of which was filed on June 30, 2000. *Id.* at 1:2–10.

“As cancer cells are actively proliferating, they require large quantities of DNA and RNA.” Ex. 1025 ¶ 67. Antifolates are a well-studied class of antineoplastic agents that inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways. Ex. 1001, 1:19–20, 1:36–41. Because antifolates interfere with DNA and RNA synthesis, antifolates are used as chemotherapeutic drugs to treat certain types of cancer. Ex. 1025 ¶ 67.

A limitation on the use of antifolate drugs is “that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients.” Ex. 1001, 1:62–64. Homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of certain antifolate enzyme inhibitors. *Id*. at 2:16–26. The ’209 patent states that folic acid has been shown to lower homocysteine levels. *Id*. Additionally, the patent states that it was known in the art to treat and prevent cardiovascular disease with a combination of folic acid and vitamin B12, but that “the use of the combination for the treatment of toxicity

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associated with the administration of antifolate drugs was unknown heretofore." *Id*. at 2:50–54.

The '209 patent describes "[a] method of administering an antifolate to a mammal in need thereof." *Id.*, Abstract. The method is said to improve the therapeutic utility of antifolate drugs by administering a methylmalonic acid ("MMA") lowering agent, such as vitamin B12, to the host undergoing treatment. *Id*. at 2:37–46. The '209 patent also states that a combination of a MMA lowering agent, such as vitamin B12, and folic acid "synergistically reduces the toxic events associated with the administration of antifolate drugs." *Id*. at 2:47–50.

The term antifolate is said to encompass chemical compounds that inhibit at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways. *Id*. at 4:28–34. Pemetrexed disodium is the most preferred antifolate for the '209 patent. *Id*. at 4:28–43. Pemetrexed is also referred to in the art as the "multitargeted antifolate" ("MTA").[2] Ex. 1022, 129,[3] Abstract 620P.

C. Illustrative Claims

Petitioner challenges claims 1–22 of the '209 patent. Claims 1 and 12 are independent, and are reproduced below:

> 1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by

[2] We use "pemetrexed" and "MTA" interchangeably throughout this Decision.

[3] We note that, unless otherwise indicated, the page numbers refer to the page numbers of the original references, and not to those added by a party.

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