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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.
and FRESENIUS KABI USA, LLC,
Petitioner,

v.

ELI LILLY & COMPANY
Patent Owner.

Case IPR2016-01341
Patent 7,772,209 B2

Before MICHAEL P. TIERNEY, JACQUELINE WRIGHT BONILLA, and TINA E. HULSE, *Administrative Patent Judges*.

TIERNEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review and Grant of Motion for Joinder
37 C.F.R. § 42.108; 37 C.F.R. § 42.122(b)

I. INTRODUCTION

Teva Pharmaceuticals USA, Inc. and Fresenius Kabi USA, LLC (collectively, "Petitioner" or "Teva"), filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent 7,772,209 B2 (Ex. 1001, "the '209 patent"). Paper 2 ("Pet."). Concurrent with the filing of the Petition, Petitioner filed a Motion for Joinder seeking to join the current proceeding to IPR2016-00237.[1] Motion for Joinder, Paper 3. Patent Owner and Petitioner filed a Joint Notice of Stipulation Concerning Joinder that states, among other things, that Patent Owner waives its right to file a Preliminary Response to the Petition. Paper 8. We have jurisdiction under 35 U.S.C. § 314.

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons set forth below, upon considering the Petition, we conclude that the information presented in the Petition establishes a reasonable likelihood that Petitioner will prevail in challenging claims 1–22 of the '209 patent. We authorize an *inter partes* review to be instituted as to those claims. Our Decision to Institute in this proceeding is consistent with our institution of *inter partes* review in IPR2016-00237. IPR2016-00237, Paper 13 ("'237 Inst. Dec.").

Additionally, all parties have stipulated that, subject to our approval, Teva shall join the proceeding with Neptune designated as Lead Petitioner and that Teva will act as a silent understudy and will not file any papers or

[1] Neptune Generics, LLC ("Neptune") v. Eli Lilly & Company ("Patent Owner"), IPR2016-00237.

exhibits in the Joined Proceeding, except *pro hac vice* motions and administrative filings. Paper 8, 2–3. For the reasons provided below, we grant Teva's Motion for Joinder and exercise our discretion to join Teva and the present proceeding to the IPR2016-00237 proceeding.

Our factual findings and conclusions at this stage of the proceeding are based on the evidentiary record developed thus far. This decision to institute trial is not a final decision as to the patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the full record developed during trial.

A. Related Proceedings

The '209 patent is the subject of litigation in the Southern District of Indiana, including *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, Case No. 1:10-cv-1376. Pet. 3–4.

The '209 patent also has been challenged in the following instituted *inter partes* reviews IPR2016-00237 and IPR2016-00240 by Neptune, and in IPR2016-00318 by Sandoz Inc. Several parties, including Petitioner, seek to join the instituted reviews. Specifically, in addition to the current case, IPR2016-01190 (Apotex) and IPR2016-01335 (Wockhardt) seek to join IPR2016-00237.[2] Also, IPR2016-01191 (Apotex), IPR2016-01337 (Wockhardt) and IPR2016-01343 (Teva) seek to join IPR2016-00240.[3]

[2] Apotex's request to join was granted. IPR2016-00237, Paper 31.

[3] Apotex's request to join was granted. IPR2016-00240, Paper 33.

Additionally, IPR2016-01429 (Apotex et. al.), IPR2016-01393 (Wockhardt) and IPR2016-01340 (Teva) seek to join IPR2016-00318. [4]

B. The ’209 Patent

The ’209 patent claims priority benefit of a series of applications, the earliest of which was filed on June 30, 2000. Ex. 1001, 1:2–10.

“As cancer cells actively proliferate, they require large quantities of DNA and RNA.” Declaration of W. Archie Bleyer, 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. As 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. *Id*. at 2:50–54.

The ’209 patent describes “[a] method of administering an antifolate to a mammal in need thereof.” Ex. 1001, abstract. The method is said to

[4] Apotex et al.’s request to join was granted. IPR2016-00318, Paper 37.

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 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 a "multitargeted antifolate" ("MTA"). Ex. 1022, 129, Abstract 620P.

C. Illustrative Claims

The '209 patent contains twenty-two claims, all of which are challenged by Petitioner. Independent claim 1 is directed to a method for administering pemetrexed disodium to a patient in need thereof, where folic acid and a MMA lowering agent, such as B12, is administered, followed by administering an effective amount of the pemetrexed disodium. Independent claim 12 is written in a Jepson claim format, where the preamble defines the admitted prior art as administering pemetrexed disodium to a patient in need of a chemotherapeutic treatment. Independent claim 12 further recites specific dosage amounts of folic acid and vitamin B12 that are administered to the patient prior to the first administration of the pemetrexed disodium. Dependent claim 2 requires the MMA lowering agent of claim 1 to be vitamin B12 and the remaining dependent claims recite various dosages of

folic acid and B12, and times for administering folic acid. Certain claims also require the administration of cisplatin to the patient.

Claims 1 and 12 are illustrative of the challenged claims 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 administering an effective amount of pemetrexed disodium, wherein
>
> the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.
>
> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
>
> a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

D. Prior Art Relied Upon

In the ground challenging the claims, Petitioner relies on the following prior art:

> Niyikiza et al., *MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity*, Annals of Oncology, Vol. 9, Suppl. 4, 1998, Abstract 609P, pg. 126 ("*Niyikiza*") (Ex. 1008)

U.S. Patent No. 5,217,974 ("*the '974 Patent*") (Ex. 1009)

European Patent Application No. 0,595,005 A1 ("*EP 005*") (Ex. 1010)

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103 based on the following ground (Pet. 27–53):

References	Basis	Claims challenged
Niyikiza in view of the '974 Patent, and further in view of EP 005	§ 103	1–22

II. ANALYSIS

A. Claim Interpretation

Petitioner identifies several claim terms in the challenged claims and provides definitions for those terms. Pet. 13–16. Patent Owner did not take a position on claim construction at this time.

We determine that it is unnecessary to construe explicitly the claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Section 103 Obviousness Challenge

Petitioner raises one challenge based on 35 U.S.C. § 103. Generally, Petitioner contends that the challenged claims merely require administering a specific antifolate cancer drug, which was known to elevate a patient's

homocysteine levels, with compounds known to decrease homocysteine levels, folic acid and vitamin B12. Pet. 17–22.

Petitioner relies upon Niyikiza as teaching one of ordinary skill in the art that MTA has activity in a variety of tumors and that toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. *Id*. at 25–26 (citing Ex. 1008, 126–27). Petitioner explains that it was known in the art that homocysteine could be reduced by two pathways, including remethylation by methionine synthase, which requires folate as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction. *Id*. at 19. Petitioner states that the '974 Patent teaches that the toxic effects of antifolate agents can be significantly reduced by pretreatment of a patient with folic acid. *Id*. at 29–33. Further, Petitioner relies upon EP 005 for its teaching that 1000 µg of folic acid and 500 µg of vitamin B12 are preferred daily dosage amounts. *Id*. at 44–45; Ex. 1025 ¶¶ 136–139. As noted above, Patent Owner waived filing a Preliminary Response.

In Neptune IPR2016-00237, we instituted *inter partes* review on the same ground, same evidence, and same claims. We incorporate our analysis from our institution decision in IPR2016-00237. '237 Inst. Dec. 11–19. For the same reasons, we determine that Petitioner has demonstrated a reasonable likelihood that it will prevail with respect to its challenge to claims 1–22 of the '209 patent.

C. Motion for Joinder

Teva seeks to join the present proceeding with IPR2016-00237. Paper 3. Teva contends that joinder is appropriate as it will promote the

efficient determination of patentability of the '209 patent without prejudice to prior Petitioners (Neptune) or Patent Owner. *Id*. at 1. Teva states that the present Petition raises the same ground of unpatentability over the same prior art as those instituted by the Board in the IPR2016-00237. *Id*. at 3. Teva represents that it is willing to agree to consolidated filings with Neptune and that joinder will not affect the pending schedule in IPR2016-00237. *Id*. at 6–8.

The parties in the present proceeding and IPR2016-00237 filed a Joint Notice of Stipulation Concerning Joinder. Paper 8. The Joint Stipulation generally provides that Neptune and Patent Owner do not oppose the joinder of the present proceeding with IPR2016-00237. *Id*. at 2. Patent Owner waives its right to file a preliminary response in the present proceeding. *Id*. As long as Neptune is not terminated as a party, Neptune will be Lead Petitioner and will conduct all argument and examination of witnesses for that side, and will submit all substantive written submissions for that side. *Id*. at 2–3. The Joint Stipulation further provides that Teva will act as a silent understudy. *Id*. at 3. The Joint Stipulation also provides that the presence of Joined Petitioners shall not be a basis for alteration of the schedule or time allotted for cross-examination, redirect, or re-cross examination of any witness. *Id*. at 4.

We hold that Petitioner has satisfied the requirements of 35 U.S.C. § 315(c) and we grant Petitioner's Motion for Joinder. We exercise our discretion and join the present *inter partes* review, IPR2016-01341, to IPR2016-00237 subject to the conditions set forth in the Joint Stipulation.

IV. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in demonstrating unpatentability of claims 1–22. The Board has not yet made a final determination of the patentability of any of claims 1–22 of the '209 patent. Additionally, for the foregoing reasons, we join the present proceeding with IPR2016-00237 subject to the conditions set forth in the Joint Stipulation.

V. ORDER

Accordingly, it is:

Ordered that Teva's Motion for Joinder is granted;

Further Ordered that the instant proceeding is instituted, joined with IPR2016-00237, and terminated under 37 C.F.R. § 42.72, and all further filings in the joined proceeding shall be made only in IPR2016-00237;

Further Ordered that trial is instituted on the grounds of unpatentability on which trial was instituted in IPR2016-00237 and that there is no change to the Scheduling Order in IPR2016-00237;

Further Ordered that the parties shall abide by the Joint Stipulation;

Further Ordered that the case caption in IPR2016-00237 shall be changed to reflect the joinder of Teva as a Petitioner in accordance with the attached example; and,

Further Ordered that a copy of this Decision shall be entered into the file of IPR2016-00237.

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