

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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NEPTUNE GENERICS, LLC,  
Petitioner,

v.

ELI LILLY & COMPANY  
Patent Owner.

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Case IPR2016-00237  
Patent 7,772,209 B2

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

TIERNEY, *Administrative Patent Judge*.

DECISION  
Institution of *Inter Partes* Review  
37 C.F.R. § 42.108

I. INTRODUCTION

Neptune Generics, LLC (“Petitioner”), 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 1 (“Pet.”). Patent Owner, Eli Lilly & Company, (“Patent Owner”) timely filed a Preliminary Response (Paper 10, “Prelim. Resp.”) to the Petition. 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 and the Preliminary Response, 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 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 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.*, et al., Case No. 1:10-cv-1376. Pet. 2, Prelim. Resp. 2.

Additionally, Petitioner notes that the '209 patent also was challenged in IPR2013-00356 by Accord Healthcare, Inc. Pet. 2.<sup>1</sup>

The '209 patent has also been challenged in IPR2016-00240 by Petitioner, and in IPR2016-00318 by Sandoz Inc.

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, 1:36–41. 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 the 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

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<sup>1</sup> The Board declined to institute in IPR2013-00356, holding that the petition was not filed within the time limit imposed by 35 U.S.C. § 315(b). *Accord Healthcare, Inc., USA v. Eli Lilly and Co.*, Case IPR2013-00356, slip op. 4 (PTAB Oct. 1, 2013) (Paper 13).

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 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 the “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  $\mu\text{g}$  and about 1000  $\mu\text{g}$  of folic acid prior to the first administration of pemetrexed disodium;
  - b) administration of about 500  $\mu\text{g}$  to about 1500  $\mu\text{g}$  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 also points us to the following prior art:

U.S. Patent No. 5,344,932 to Edward C Taylor, issued on Sep. 6, 1994 (“*Taylor*”) (Ex. 1003)

Worzalla et al., *Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514*, *Anticancer Research* 18:3235-3240 (1998) (“*Worzalla*”) (Ex. 1005)

U.S. Patent No. 4,140,707 to Cleare et al., issued on Feb. 20, 1979 (“*Cleare*”) (Ex. 1006)

Tsao CS, *Influence of Cobalamin on the Survival of Mice Bearing Ascites Tumor*, *Pathobiology* 1993;61:104-108 (“*Tsao*”) (Ex. 1007)

Rusthoven et al., *Multitargeted Antifolate LY231514 as First-Line Chemotherapy for Patients with Advanced Non-Small-Cell Lung Cancer: A Phase II Study*, *Journal of Clinical Oncology*, Vol. 17, No. 4, (April 1999), pp. 1194-1199 (“*Rusthoven*”) (Ex. 1011)

Refsum H & Ueland PM, *Clinical significance of pharmacological modulation of homocysteine metabolism*, *Trends in Pharmacol. Sci.*, Vol. 11, No. 10, 1990, pp. 411-416 (“*Refsum*”) (Ex. 1012)

Calvert AH & Walling JM, *Clinical studies with MTA*, British Journal of Cancer (1998) 78 (Suppl. 3), 35-40 (“*Calvert 1998*”) (Ex. 1013)

Calvert H, *An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents*, Seminars in Oncology, Vol. 26, No. 2, Suppl 6 (April), 1999, pp. 3-10 (“*Calvert 1999*”) (Ex. 1014)

O’Dwyer et al., *Overview of Phase II Trials of MTA in Tumors*, Seminars in Oncology, Vol. 26, No. 2, Suppl 6 (April), 1999, pp. 99-104 (“*O’Dwyer*”) (Ex. 1015)

Zervos et al., *Functional folate status as a prognostic indicator of toxicity in clinical trials of the multitargeted antifolate LY231514*, Proceedings of ASCO, Vol. 16, 1997, pg. 256a (“*Zervos*”) (Ex. 1016)

Allen et al., *Diagnosis of Cobalamin Deficiency I: Usefulness of Serum Methylmalonic Acid and Total Homocysteine Concentrations*, American Journal of Hematology, 34, 1990, 90- 98 (“*Allen*”) (Ex. 1017)

Savage et al., *Sensitivity of Serum Methylmalonic Acid and Total Homocysteine Determinations for Diagnosing Cobalamin and Folate Deficiencies*, The American Journal of Medicine, 96: 1994, 239-246 (“*Savage*”) (Ex. 1018)

Brönstrup et al., *Effects of folic acid and combinations of folic acid and vitamin B-12 on plasma homocysteine concentrations in healthy, young women*, Am. J. Clin. Nutr. Vol. 68, 1998, 1104-10 (“*Bronstrup*”) (Ex. 1019)

Carrasco et al., *Acute megaloblastic anemia: homocysteine levels are useful for diagnosis and follow-up*, Haematologica, Vol. 84(8), August 1999, 767-768 (“*Carrasco*”) (Ex. 1020)

Thödtmann et al., *Phase I study of different sequences of MTA (LY231514) in combination with cisplatin in patients with solid tumours*, Annals of Oncology, Vol. 9, Suppl. 4, 1998, Abstract 618P, pg. 129 (“*Thodtmann*”) (Ex. 1021)

Hammond et al., *A Phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)*, Annals of

Oncology, Vol. 9, Suppl. 4, 1998, Abstract 620P, pg. 129 (“*Hammond*”) (Ex. 1022)

Morgan et al., *The Effect of Folic Acid Supplementation on the Toxicity of Low-Dose Methotrexate in Patients with Rheumatoid Arthritis*, *Arthritis and Rheumatism*, Vol. 33, No. 1, January 1990, pp. 9-18 (“*Morgan*”) (Ex. 1023)

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103 based on the following ground (Pet. 25–51):

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

E. Level of Ordinary Skill in the Art

Petitioner’s declarant, Dr. W. Archie Bleyer, testifies that, a person of ordinary skill in connection with the ’209 patent would have had an M. D. degree with significant experience in treating cancer patients, including an understanding of antineoplastic agents, such as antifolates and their efficacies, safety, adverse effects, toxicities, etc. (Ex. 1025, ¶ 20). Additionally, Dr. Bleyer testifies that a person of ordinary skill in the art may work as part of a multi-disciplinary team. *Id.* at ¶ 21. At this stage of the proceeding, Patent Owner does not dispute this recitation of the level of ordinary skill in the art. We adopt the level of ordinary skill in the art identified by Dr. Bleyer, as it is consistent with the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).



## II. PRIOR LITIGATION

Patent Owner does not address the merits of the Petition, but contends that the Petition should be denied because a district court has already considered and rejected similar arguments in its decision on validity of claims 9, 10, 12, 14, 15, 18, 19, and 21. Prelim. Resp. 1, 5–10, citing Ex. 1028 (“Findings of Fact and Conclusions of Law Following Bench Trial August 19, 2013”). Patent Owner contends that the prior district court decision currently is pending before the Federal Circuit and will precede any ruling by the Board. *Id.* at 11–12. Patent Owner argues that the upcoming Federal Circuit decision will be dispositive of the issues raised by Petitioner. *Id.* at 12–17.

We have considered Patent Owner’s contentions but do not find them persuasive on this record. Patent Owner does not contend that Petitioner is barred from raising its specific challenges before this tribunal. Also, the district court decision did not address the patentability of claims 1–8, 11, 13, 16, 17, 20 and 22. Ex. 1028. Further, the district court’s analysis focused on “Worzalla and Hammond as prior art” and “’974 Patent as prior art,” and relied heavily on the testimony of Patent Owner’s experts, Drs. Chabner and Zeisel. Ex. 1028, 10–16. In contrast, the challenge raised in this proceeding focuses on the Niyikiza reference in combination with the ’974 patent and EP 005, where the testimonial evidence presented is distinct from that in the district court. Pet. 25–51. Specifically, Petitioner’s expert, Dr. Bleyer, does not appear to have testified in the district court proceeding, and Patent Owner has not submitted testimony in this proceeding from Drs. Chabner and Zeisel.

Based upon the facts presented, we are not persuaded that the decision by the Federal Circuit will dispose of the issues raised in the Petition. *In re*

*Swanson*, 540 F.3d 1368, 1377 (Fed. Cir. 2008) (A finding that a patent is valid operates only on the parties and does not extend from one case to the next. A future challenger with new or better information may subsequently raise, and succeed on invalidity).

### III. MERITS ANALYSIS

#### A. Claim Interpretation

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner identifies several claim terms in the challenged claims and provides definitions for those terms. Pet. 12–14. 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. 15–20. Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–22 are unpatentable as obvious over the cited art.

1. Background on Obviousness

An invention is not patentable under 35 U.S.C. § 103 if it is obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). Under § 103:

the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

*Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In addressing the findings of fact, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. As explained in *KSR*:

If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

*Id.* at 417. Accordingly, a central question in analyzing obviousness is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.*

## 2. The Prior Art References

### a. Niyikiza (Ex. 1008)

Niyikiza states that MTA (pemetrexed) is a multitargeted antifolate with inhibitory activity against multiple enzymes. Ex. 1008, 126, Abstract 609P. Niyikiza describes treating 139 patients with tumors in a Phase II study with MTA and monitoring the patients for homocysteine, cystathionine and methylmalonic acid (“MMA”) levels. *Id.* Toxicities resulting from the MTA treatment were found to be predictable from pretreatment homocysteine levels. *Id.* at 127. Niyikiza states that further studies are underway in patients with renal impairment or patients who received prior cisplatin. *Id.*

### b. The '974 Patent (Ex. 1009)

The '974 Patent describes the administration of a folate binding protein binding agent in conjunction with the use of an antifolate. Ex. 1009, abstract, 1:54–58, 2:60–65. The folate binding agent is administered to a mammal prior to treatment with the antifolate. *Id.* at 6:22–24. A preferred embodiment involves administering about 1 mg to about 5 mg of folic acid as the folate binding agent, with the folic acid administered orally about 1 to 24 hours prior to treatment with lometrexol (an antifolate). *Id.* at 6:37–42.

Multiple doses of folic acid may be made up to weeks before treatment to ensure that folate binding protein is sufficiently bound. *Id.* at 6:32–37.

c. EP 005 (Ex. 1010)

EP 005 describes pharmaceutical preparations for lowering blood and tissue levels of homocysteine and counteracting harmful effects associated with homocysteine. Ex. 1010, 2:1–3. Elevated homocysteine levels are highly undesirable and normalization of elevated levels constitutes a therapeutic goal. *Id.* at 3:7–9.

Three pathways are said to exist to control homocysteine including remethylation to methionine, which requires folate and vitamin B12 as a co-factor. *Id.* at 2:25–30. EP 005 identifies a number of publications that are said to describe the relationship between B12 and folate levels individually and blood levels of homocysteine. *Id.* at 3:37–45. EP 005 seeks to lower total homocysteine blood levels elevated by any known cause, including drugs that induce elevated homocysteine levels, such as methotrexate, a well-known antifolate. *Id.* at 4:43–48.

EP 005 discloses a pharmaceutical preparation comprising vitamin B6, folate and vitamin B12, for prophylaxis or treatment of elevated levels of homocysteine in a patient. *Id.* at 4:37–42. According to EP 005, for purposes of controlling blood homocysteine levels, the combination of folate, vitamin B12 and B6 produces advantageous effects and provides an unexpected synergism that goes substantially beyond what would be expected from a simple additive effect of the action of these compounds. *Id.* at 11:20–25. A suitable daily dosage of the pharmaceutical preparation is described as:

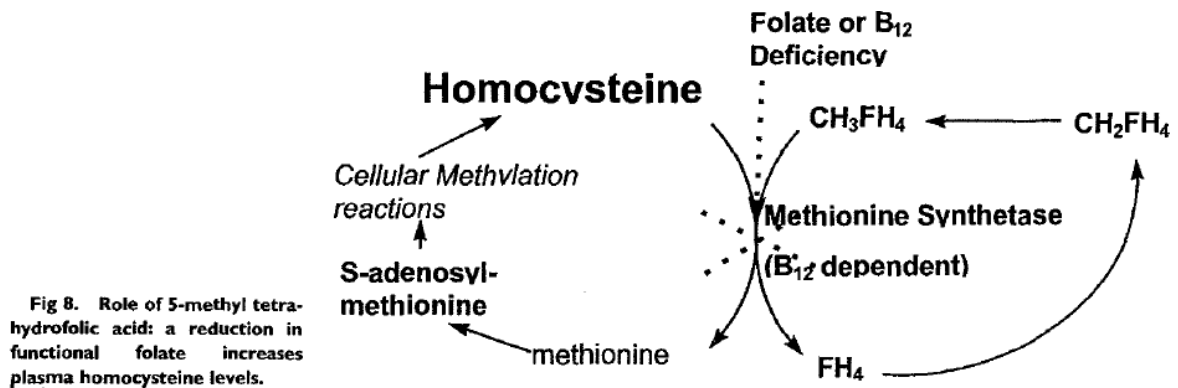
Formulation type	PL		Folate		B12	
	Range mg	Preferred mg	Range mg	Preferred mg	Range mg	Preferred mg
Normal (no absorption problem)	2-5	5	0,2-15	1,0	0.1-2	0.5
Special (to overcome absorption problems)	2-50	5	2-15	5	0.2-5	1,0

*Id.* at 8:14–51. As represented in the chart above, PL (pyridoxal) is the preferred form of vitamin B6. *Id.* at 6:12–17.

d. Calvert 1999 (Ex. 1014)

As background regarding what an ordinary artisan would have known when reading the prior art references discussed above, Petitioner points to Calvert 1999. Pet. 15–17. Calvert 1999 provides an overview of folate metabolism and describes features relevant to the action and toxicities of antifolate cancer agents. Ex. 1014, 3. According to Calvert 1999, the development of cancer therapeutics has been linked intimately to the study of folic acid metabolism and the action of antifolate drugs. *Id.* Calvert 1999 depicts the chemical structures of various antifolates, including methotrexate, lometrexol and MTA. *Id.* at 6. Folic acid supplementation is said to reduce the toxicity of antifolate drugs. *Id.* at 8. Calvert 1999 also discusses, however, how it had been difficult to correlate antifolate-induced toxicity with pretreatment folate levels. *Id.*

Calvert 1999 teaches that intracellular homocysteine can be reduced by converting it to methionine through remethylation by methionine synthase. *Id.* at 8–9. As depicted below, methionine synthase requires folate (5-methyltetrahydrofolate) as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction:



*Id.* at 9. Calvert 1999 states that an increase in the plasma level of homocysteine occurs when there is a functional deficiency in either B12 or folate. *Id.*

### 3. Independent Claims 1 and 12

Generally, Petitioner contends that it was well known in the art that antifolates, such as MTA, had anticancer properties, and that it was known that toxicity had limited the administration of antifolates, such as methotrexate and MTA. Pet. 15–16. 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 26–27 (citing Ex. 1008, 126–7).

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 17. 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 27–28 and 33–34.

Petitioner also states that EP 005 teaches that one skilled in the art can control drug-induced homocysteine levels, including antifolate drug induced levels, by pretreatment with a combination of folic acid, vitamin B12 and vitamin B6. *Id.* at 22–23, 27–29 and 33–39. Petitioner relies upon the testimony of Dr. Bleyer to support its contention that pretreating an MTA patient with folic acid and vitamin B12 was suggested by the prior art, which recognized the benefit of the combination of folic acid and vitamin B12 for controlling homocysteine levels in antifolate patients. Pet. 15–39, Ex. 1025. Further, Petitioner relies upon EP 005 for its teaching that 1000 mg of folic acid and 500 mg of vitamin B12 are preferred daily dosage amounts. *Id.* at 42–43; Ex. 1025 ¶¶ 136–139. As noted above, Patent Owner chose not to address the merits of the Petition in its Preliminary Response. Paper 10, 1 n.1.

Based upon the record presented, we credit Dr. Bleyer's testimony as follows. On this record we find that Niyikiza demonstrates that MTA was a known antifolate cancer treatment agent. Ex. 1025 ¶¶ 98–100. We also find that that Niyikiza teaches one skilled in the art at the time of the invention that a significant correlation existed between MTA toxicity and increased



homocysteine levels. *Id.* ¶ 99. On this record, we find that the '974 Patent and EP 005 would have led one of ordinary skill in the art to understand that pretreatment with folic acid and vitamin B12 would stimulate recycling of methionine in the body and control homocysteine levels. *Id.* ¶¶ 102–108. We also credit Dr. Bleyer's testimony, as it is consistent with the references of record.

Based upon the record presented, we conclude that Petitioner has shown a reasonable likelihood of prevailing in its assertion that independent claims 1 and 12 are unpatentable over Niyikiza, the '974 Patent, and EP 005. Specifically, Petitioner has established sufficiently that administering folic acid and vitamin B12 followed by the administration of MTA to a patient in need represents a combination of known treatments, used for their known purpose (treating cancer patients, controlling homocysteine levels) to achieve a predictable result (controlling homocysteine levels in a cancer patient). *Id.* ¶ 148.

#### 4. Dependent Claims 2–11, 13–22

Dependent claims 2–11 and 13–22 generally recite various dosages of folic acid and B12, as well as times for administering folic acid. Certain dependent claims require the administration of cisplatin to the patient. For example, dependent claim 13 further requires the administration of cisplatin, and dependent claim 14 requires vitamin B12 be administered as an intramuscular injection of about 500 µg to about 1500 µg.

Petitioner contends that the dependent claims merely add limitations already known in the field and would have been obvious to one of ordinary skill in the art. Pet. 39–51. According to Petitioner, it would have been obvious to administer the specific dosage amounts recited in the claims, as EP 005 discloses amounts falling within the claimed range as effective amounts to control homocysteine levels. *Id.* at 39–48. Petitioner also relies upon EP 005 for its teaching that vitamin B12 and folic acid may be administered via intramuscular injection. *Id.* at 42. As to the timing of the dosages, Petitioner contends that EP 005 teaches that its pharmaceutical preparations are made available on a timed program dosage regime, which provides for different dosages during different periods over the course of treatment and one skilled in the art would have adjusted the program to the clinical condition of the patient. *Id.* at 43–44; Ex. 1025 ¶ 152. Petitioner further states that one skilled in the art would have recognized the benefit of administering cisplatin with MTA, as Niyikiza discloses studies with MTA and cisplatin administration. Pet. 49–50; Ex. 1025 ¶ 166. Petitioner’s contentions are supported by the declaration of Dr. Bleyer, whose testimony on this record is consistent with the teachings of the cited references. As mentioned above, Patent Owner chose not to address the merits of the Petition in its Preliminary Response. Paper 10, 1 n.1.

Based on the record presented, Petitioner has shown a reasonable likelihood of prevailing in its assertion that dependent claims 2–11 and 13–22 are unpatentable over Niyikiza, the ’974 Patent and EP 005. Specifically, Petitioner has established sufficiently that administering folic acid and vitamin B12 in the

specified ranges followed by the administration of MTA, alone or with cisplatin, to a patient in need represents a combination of known treatments using known ranges, used for their known purpose (treating cancer patients, controlling homocysteine levels) to achieve a predictable result (controlling homocysteine levels in a cancer patient). Ex. 1025 ¶¶ 149–169.

#### IV. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition, notwithstanding the Preliminary Response, 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.

#### V. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–22 of the '209 patent on the following ground:

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

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FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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