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Filed: June 30, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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WOCKHARDT BIO AG

PETITIONER

V.

ELI LILLY & COMPANY

PATENT OWNER

_____

CASE NO.: UNASSIGNED
PATENT NO. 7,772,209

_____

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,772,209 UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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I. INTRODUCTION

On June 3, 2016, the Board instituted *Inter Partes* Review ("IPR") of claims 1-22 of U.S. Patent No. 7,772,209 ("the '209 Patent") (Ex. 1001) in IPR2016-00237. In its decision of institution, the Board determined that it is reasonably likely that claims 1-22 would have been obvious in view of the following references: (1) 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); (2) U.S. Patent No. 5,217,974 ("*the '974 Patent*") (Ex. 1009); and (3) European Patent Application No. 0,595,005 AI ("*EP 005*") (Ex. 1010). *Neptune Generics, LLC v. Eli Lilly & Company*, Paper 13 at 18-19 (PTAB June 3, 2016).

Wockhardt Bio AG ("Wockhardt") submits this Petition for IPR ("Petition") also seeking cancellation of claims 1-22 of the '209 Patent as unpatentable under 35 U.S.C. section 103(a) over Niyikiza in view of the '974 Patent, and further in view of EP 005. This petition presents the same arguments, based on the same prior art presented in the IPR2016-00237 Petition (IPR2016-00237, Paper 1), and on which the Board instituted IPR in IPR2016-00237, along with a Motion for Joinder to join this Petition with the IPR2016-00237

proceedings. Indeed, this petition is an almost verbatim copy of the petition in IPR2016-00237[1].

For the reasons explained below, and for the reasons the Board instituted IPR in IPR2016-00237, Wockhardt is reasonably likely to prevail on Ground 1 with respect to the challenged claims. Wockhardt requests that this Board institute IPR and cancel each of claims 1-22 of the '209 Patent.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Pursuant to 37 C.F.R. § 42.104(a), Wockhardt certifies that the '209 Patent is available for IPR and that Wockhardt is not barred or estopped from requesting IPR challenging the claims of the '209 Patent on the grounds identified in this Petition.

III. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

In accordance with 37 C.F.R. § 42.8(b)(1), Petitioner identifies the real party-in-interest as Wockhardt Bio AG, Wockhardt Limited, Wockhardt USA LLC, and Morton Grove Pharmaceuticals, Inc. (collectively "Wockhardt").

[1] Wockhardt's intention is to copy the relevant portions of IPR2016-00237 verbatim. To the extent discrepancies exist between the respective petitions, those differences are due to solely to transcription errors.

B. Related Judicial and Administrative Matters (37 C.F.R. § 42.8(b)(2))

Pursuant to 37 C.F.R. § 42.8(b)(2), Wockhardt states that the '209 Patent has been the subject of the following lawsuits: *Eli Lilly and Company v. Biocon Limited*, INSD-1:16-cv-00469 (filed Feb 26, 2016); *Eli Lilly and Company v. Dr. Reddy's Laboratories, Ltd. et al.*, INSD-1:16-cv-00308 (filed Feb. 5, 2016); *Petition for Inter Partes Review by Sandoz Inc.*, PTAB-IPR2016-00318 (filed Dec. 14, 2015); *Petition for Inter Partes Review by Neptune Generics,* LLC, PTAB-IPR2016-00237 (filed Nov. 24, 2015); *Petition for Inter Partes Review by Neptune Generics, LLC*, PTAB-IPR2016-00240 (filed Nov. 24, 2015); *Eli Lilly and Company v. Fresenius Kabi USA, LLC*, INSD-1:15-cv-00096 (filed Jan. 23, 2015); *Eli Lilly and Company v. Sandoz Inc.*, INSD-1:14-cv-02008 (filed Dec. 5, 2014); *Eli Lilly and Company et al. v. Nang Kuang Pharm. Co., Ltd. et al.*, INSD-1:14-cv-01647 (filed Oct. 8, 2014); *Eli Lilly and Company v. Glenmark Pharm. Ltd. et al.*, INSD-1:14-cv-00104 (filed Jan. 23, 2014); *Eli Lilly and Company v. Sun Pharm. Global FZE et al.*, INSD-1:13-cv-01469 (filed Sept. 13, 2013); *Petition for Inter Partes Review by Accord Healthcare, Inc.*, PTAB-IPR2013-00356 (filed June 14, 2013); *Eli Lilly and Company v. Accord Healthcare, Inc., USA*, INSD-1:13-cv-00335 (filed Feb. 28, 2013); *Eli Lilly and Company v. Apotex, Inc. et al.*, INSD-1:12-cv-00499 (filed Apr. 17, 2012); *Eli Lilly and Company v. Accord Healthcare, Inc., USA*, INSD-1:12-cv-00086 (filed Jan. 20, 2012); *Eli Lilly and Company v.*

App Pharm., LLC, INSD-1:11-cv-00942 (filed Jul. 15, 2011); and *Eli Lilly and Company v. Teva Parental Medicines, Inc., et al.*, INSD-1:10-cv-01376 (filed Oct. 29, 2010).

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

In accordance with 37 C.F.R. § 42.8(b)(3), Petitioner identifies Patrick A. Doody as lead counsel and Bryan P. Collins as back-up counsel. Concurrently filed is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b).

In accordance with 37 C.F.R. § 42.8(b)(4), Petitioner identifies the following service information:

Lead Counsel	**Back-up Counsel**
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Wockhardt consents to electronic service.

IV. PAYMENT OF FEES (37 C.F.R. § 42.15(a) and § 42.103)

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the

Office is authorized to charge such fees to Deposit Account No. 033975. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of U.S. Patent No. 7,772,209

The '209 Patent is titled "Antifolate Combination Therapies." (Ex. 1001 at Front Cover.) The underlying application, U.S. Patent App. No. 11/776,329 (the "'329 Application"), was filed on July 11, 2007. The '209 Patent issued to Clet Niyikiza on August 10, 2010. (*Id.*) The earliest application to which the '209 Patent claims priority is U.S. Patent App. No. 60/215,310 (filed June 3, 2000).

1. The '209 Patent Specification

The '209 Patent claims "a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP [folate binding protein] binding agent." (*Id.* at 3:1–5.) "A preferred FBP binding agent is folic acid," and a preferred methylmalonic acid ("MMA") lowering agent is vitamin B12. (*Id.* at 3:5–6, 4:47–50.)

The '209 specification admits the following with respect to the prior art:

> Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective

chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer.

(*Id*. at 1:19–25.) The ’209 specification states that “life-threatening toxicity remains a major limitation to the optimal administration of antifolates,” while admitting that increased homocysteine levels have been known to cause antifolate toxicity. (*Id.* at 1:11–13, 2:24–26.) The specification also admits that “[f]olic acid has been shown to lower homocysteine levels.” (*Id.* at 2:16–17.) And, it admits that “increased levels of methylmalonic acid is a predicator of toxic events in patients that receive an antifolate drug,” and further admits that treatment with vitamin B12 was known to reduce those toxic events: “the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known….” (*Id.* at 2:41–43, 50–52.)

The ’209 Patent’s purported invention was designed “to lower cytotoxic activity” associated with antifolate treatment. (*Id.* at 2:29–37.) The patent states that “we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs.” (*Id.* at 2:47–50.)

The ’209 Patent’s invention can be summarized as: (1) administration of pemetrexed disodium to a patient in combination with an effective amount of folic acid and an effective amount of MMA lowering agent, such as vitamin B12; (2)

pretreatment with folic acid prior to pemetrexed disodium treatment; (3) pretreatment with folic acid and vitamin B12 prior to pemetrexed disodium treatment; (4) repetition of vitamin B12 administration; and (5) administering cisplatin with pemetrexed disodium to the patient. (*Id.* at 10:56–12:29.)

The patent also states that a physician determines the amount of MMA lowering agent to be administered based on "the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms…." (*Id.* at 5:37–50; 6:41–52.)

2. The '209 Patent Claims

The '209 Patent has two independent claims (Claims 1 and 12) and 20 dependent claims. Claim 1 provides:

> 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.

(*Id.* at 10:56–65.)

Claim 12 provides:

> 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.

(*Id.* at 11:25–12:4.)

3. The ’209 Prosecution History

During prosecution of the ’329 Application, the Examiner initially rejected all claims as obvious under 35 U.S.C. § 103(a) over *Taylor* (Ex. 1003) in view of *Poydock*, and in further view of *Worzalla* (Ex. 1005) and *Cleare* (Ex. 1006). (Ex. 1002 at 310.) At the time of this rejection, Claims 40–52 were pending. (*Id.* At 307.) Claim 40, the only independent claim, recited “[a] method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of pemetrexed disodium in combination with a methylmalonic acid lowering agent….” (*Id.* at 345.)

The Examiner rejected Claims 40–52, stating that *Taylor* taught “N-(pyrrolo(2,3-D)pyrimidin-3-ylacyl)-glutamic acid derivatives,” including pemetrexed (LY 231514) and pemetrexed disodium, as effective antineoplastic

agents for inhibition of tumor growth, where other antineoplastic agents could be combined with pemetrexed, while *Poydock* taught "a methylmalonic acid lowering agent such as hydroxocobalamin" for inhibition of tumors implanted in mice. (*Id.* at 310–11.) The Examiner further stated that *Worzalla* taught "the supplementation of folic acid with LY 231514 to enhance LY 231514 antitumor activity," while *Cleare* taught "malonato platinum anti-tumor compounds such as cisplatin to treat malignant tumors." (*Id.* at 311.) The Examiner concluded that "one skilled in the art would have assumed the combination of three antineoplastic agents into a single composition would give an additive effect in the absence of evidence to the contrary." (*Id.*) The Examiner further stated that although the cited references do not teach the dosage range for the MMA lowering agent, "those skilled in the art would have [] readily optimized effective dosages and concurrent administration dosage forms as determined by good medical practice and the clinical condition of the individual patient." (*Id.* at 311.)

In response, Applicant amended Claim 45 by disclosing a "specific folic-binding-protein binding agent species recited in the specification," and amended Claim 40 by adding, among other limitations, "lowering agent." (*Id.* at 188.) Applicant also argued that *Poydock* was "discredited prior to the present application's priority date" because, shortly after publication, it was discovered that MMA lowering agent did not possess antitumor activity. (*Id.* at 188–89.)

In response, the Examiner rejected the claims as obvious over *Taylor* in view of *Tsao* (Ex. 1007), and in further view of *Worzalla* and *Cleare*. (Ex. 1002 at 108.) The Examiner stated *Tsao* teaches "a methylmalonic acid lowering agent such as cobalamin (vitamin B12) is effective as having antitumor activity," and maintained rejections with respect to *Taylor*, *Worzalla*, and *Cleare*. (*Id.* at 108–09.)

Applicant then canceled Claims 45–46, added new Claims 53–63, and amended Claim 40 by adding, among other limitations, "administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by." (*Id.* at 82–85.) Applicant argued that the Examiner misinterpreted "the art concerning vitamin B12 antineoplastic activity and the teachings of [*Taylor*]." (*Id.* at 86.) Applicant also argued that the Examiner overstated *Tsao*'s teachings because *Tsao* disclosed results from hospital surveys and animal studies with conflicting results on the effectiveness of vitamin B12 therapy alone or in combination with chemotherapeutic agents and "cyanocobalamin 'did not affect cell growth at a daily dose as high as 1,000 mg/kg body weight.'" (*Id.* at 86–87.) Thus, "a person of ordinary skill in the art reading *Tsao*, would not have perceived a reasonable expectation of success in making Applicant's invention in view of the scientific uncertainty concerning vitamin B12 and its use as an antitumor agent." (*Id.* at 87.)

Applicant further submitted "that the activity of B12 as a potential antitumor therapeutic is still inconclusive even as of today." (*Id.*) Applicant argued that pemetrexed disodium, a folate analog, as a multitargeted antifolate with specific activity at three enzymes in the biosynthesis of nucleic acids—"dihydrofolate reductase (DHFR), thymidine synthase (TS), and GAR formyltransferase (GARFT)"—competes with folate at each of the enzymes' folate binding sites. (*Id.* at 88.) Applicant additionally argued that "[i]f there is an excess of the natural ligand (the natural folate source) for the three enzymes then the effectiveness of pemetrexed disodium is reduced." (*Id.*)

Applicant also argued that "[a]t the time of the invention, the skilled artisan would have been aware it was standard of care to avoid vitamins in patients undergoing chemotherapy, because the usage of vitamins could decrease the effectiveness of the chemotherapy." (*Id.*) Applicant then stated that AstraZeneca's compound Tomudex® (TS inhibitor), if administered with folic or folinic acid, may impair its cytotoxic action; "[v]itamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate" (DHFR inhibitor); and fluorouracil (5-FU), if administered with folinic acid, increases toxicity. (*Id.* at 88–89.) Further, Applicant argued that "[t]he 1999 monograph from the 'Physicians' Desk References' describes leucovorin," a folic

acid derivative, counteracts "the therapeutic and toxic effects of folic acid antagonists such as methotrexate." (*Id.* at 89.) Applicant additionally argued:

> Applicants unexpectedly discovered administering vitamin B12 and folic acid as claimed reduces toxicity of pemetrexed disodium. … The specification also explains that pilot studies in humans established that vitamin B12 given to patients receiving ALIMTA experienced fewer side effects. Clinical studies sponsored by Eli Lilly (Lilly) confirmed less overall pemetrexed disodium-related toxicity. … Applicants have made a significant discovery not obvious in view of the references cited in the Office Action. A skilled artisan would not have expected the reduction of severe toxicities associated with pemetrexed disodium administration, such as patient death, without reduction of pemetrexed disodium's efficacy. … Therefore, the rejection is clearly improper and should be withdrawn."

(*Id.* at 89–91.)

Finally, Applicant argued that the Examiner misinterpreted *Worzalla*'s teachings because *Worzalla* discloses that "the addition of folic acid may reduce effectiveness of pemetrexed disodium," and "provides no suggestion that lowering methylmalonic acid levels would further reduce associated toxicities while maintaining the therapeutic efficacy of pemetrexed disodium." (*Id.* at 91.) Further, Cleare "does not disclose or provide rationale for the combination of platinum anti-tumor compounds with Applicant's claimed method of treating patients with pemetrexed disodium." (*Id.*) Applicant then argued:

> [T]he Examiner's allegation that "readily optimized effective and concurrent administration dosage forms" are available in the art or are within "the ability of tasks routinely performed ... without undue experimentation" does not rise to the level of "supporting objective evidence" under Application of Lunsford. … [T]he Examiner could not arrive at the presently claimed invention, its dosing ranges and/or its cyclic administration.

(*Id.* at 92.)

After responding to an additional double-patenting rejection, all of the '209 Patent claims were allowed. (*Id.* at 45, 47.)

B. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279 (Fed. Cir. 2015). The broadest reasonable construction of claim language is not one that permits any reading, but instead is one that must be made "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004) (citation omitted). Unless otherwise noted, Wockhardt contends that the claim terms of the '209 Patent are

presumed to take on the ordinary and customary meaning that they would have to one of ordinary skill in the art.[2]

1. "Patient"

"Patient" means "a human undergoing medical treatment." (Ex. 1026 at 9, 13; Ex. 1025 ¶ 59.) Teva has previously proposed this same construction with respect to the '209 Patent. (Ex. 1026 at 9.)

2. "Methylmalonic acid lowering agent"

"Methylmalonic acid lowering agent" means "vitamin B12 or its derivative that lowers the concentration of methylmalonic acid in a mammal." (Ex. 1001 at 4:47–50; Ex. 1025 ¶ 60.) Teva has previously proposed a similar construction with respect to the '209 Patent. (Ex. 1027 at 2.)

3. "An effective amount of pemetrexed disodium"

"An effective amount of pemetrexed disodium" means "an amount of pemetrexed disodium that is capable of providing a therapeutic benefit to the patient in need thereof." (Ex. 1001 at 3:53–58; Ex. 1025 ¶ 61.) Teva has previously proposed this same construction with respect to the '209 Patent. (Ex. 1027 at 2.)

[2] Wockhardt notes that, in some instances, the patentee has defined claim terms apart from their plain meaning. *See Pacing Techs., LLC v. Garmin Int'l, Inc.*, 778 F.3d 1021, 1024 (Fed. Cir. 2015). These terms include "inhibit," "nonhematologic event," "in combination with," "methylmalonic acid," "MMA," "vitamin B12," "FBP binding agent," "physiologically–available salt," and "pharmaceutical." (Ex. 1001 at 3:49–52, 4:1–3, 4:4–27, 5:5–10, 5:51–6:5, 6:6–12; 6:53–54.)

4. "An effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent"

"An effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent" mean "amounts of folic acid and a methylmalonic acid lowering agent that are capable of reducing the prevalence or severity of one or more toxicities associated with the administration of pemetrexed disodium." (Ex. 1001 at 3:53–58; Ex. 1025 ¶ 62.) Teva has previously proposed this same construction with respect to the '209 Patent. (Ex. 1027 at 1.)

5. "Toxicity"

"Toxicity" means "a toxic event associated with the administration of an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, mucositis, liver dysfunction diarrhea, fatigue, anorexia, nausea, vomiting, skin rash, immunosuppression, infection, diarrhea, and anemia and toxic death." (Ex. 1025 ¶ 63; Ex. 1001 at 3:59–67.)

6. "Antifolate" and "antifolate drug"

"Antifolate" and "antifolate drug" mean "'a chemical compound which inhibits at least one key folate requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ('TS'), dihydrofolate reductase ('DHFR'), or glycinamide ribonucleotide formyltransferase ('GARFT'), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates' include methotrexate, Tomudex® Lometrexol®,

pyrido[2,3-d]pyrimidine derivatives, and 'derivatives described by Akimoto in US. Pat. No. 4,997,838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed Disodium (ALIMTA), as manufactured by Eli Lilly & Co.'" (Ex. 1025 ¶ 64; Ex. 1001 at 4:28–44.)

C. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Wockhardt requests IPR under 35 U.S.C. § 311 of Claims 1–22 of the '209 Patent, and cancellation of these 22 claims as unpatentable.

2. Statutory Grounds of Challenge

Wockhardt requests IPR of Claims 1–22 of the '209 Patent in view of the following references, each of which is prior art to the '209 Patent under 35 U.S.C. § 102(b). None of the prior art listed in the following chart was before the Examiner during prosecution of the '209 Patent. (See Ex. 1001 References Cited.) Claims 1–22 are unpatentable under 35 U.S.C. § 103:

Ground	Proposed Rejections for the '209 Patent	Exhibit Number(s)
1	Claims 1–22 are obvious under 35 U.S.C. § 103(a) in view of *Niyikiza* (Ex. 1008), U.S. 5,217,974 (the "*'974 Patent*") (Ex. 1009), and EP 0 595 005 ("*EP 005*") (Ex. 1010).	1008, 1009, and 1010

D. Overview of the State of the Art and Motivation to Combine

By June of 1999—the earliest possible priority date for the '209 Patent—it was well known in the art that antifolates such as pemetrexed had anticancer properties. (Ex. 1013 at 35; Ex. 1008 at 126; Ex. 1011 at 1194; Ex. 1014 at 3; Ex. 1015 at 99.) Antifolates inhibit folate-dependent enzymes, particularly enzymes involved in the synthesis of precursors of DNA. (Ex. 1013 at 35.) As cancer cells actively proliferate, "they require large quantities of DNA and RNA," and antifolates interfere with DNA and RNA synthesis because of their structural similarities to DNA precursors, causing cell death or stasis. (*Id.*) However, antifolates act on all proliferating cells, not just actively proliferating cancer cells, causing severe antifolate-associated side effects (i.e., toxicity). (*Id.*) Some of these toxic effects are related to haematopoietic system and epithelial cells, which are severe and even life-threatening. (*Id.*)

Pemetrexed, a multi-targeted antifolate ("MTA"), is a folate analog that inhibits several enzymes in the folate pathway, such as TS, GARFT, DHFR, and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT). (*Id.*) Prior to 1999, several Phase I and Phase II trials were conducted with pemetrexed to treat solid tumors, particularly breast, pancreatic, colorectal, and non-small-cell lung ("NSCLC") cancers. (*Id.* at 38; 1015 at 99.) However, it was known from the

prior art that toxicity has limited the administration of antifolates, such as methotrexate and pemetrexed. (Ex. 1008 at 126, Ex. 1001 at 1:62–64.)

By June 1999, extensive research into antifolate toxicity indicated that elevated levels of blood homocysteine were observed in patients treated with antifolate, such as pemetrexed. (Ex. 1001 at 2:14–26; Ex. 1014 at 8–9, Ex. 1016 at 256a.) These studies showed that folic acid supplementation reduced antifolate toxicity by lowering elevated homocysteine levels. (Ex. 1010 at 4; see also Ex. 1016 at 256a.)

It was also known in the art by June 1999 that the intracellular homocysteine can be reduced by two pathways: (a) salvage to methionine through remethylation by methionine synthase, and (b) conversion to cysteine via the trans-sulfuration pathway. (Ex. 1012 at 411.) Methionine synthase requires folate (5-methyltetrahydrofolate) as a methyl donor and vitamin B12 as a cofactor for the remethylation reaction. (*Id.*; Ex. 1014 at 8–9.) *Calvert*'s figure, depicting remethylation of homocysteine to methionine, is reproduced below:

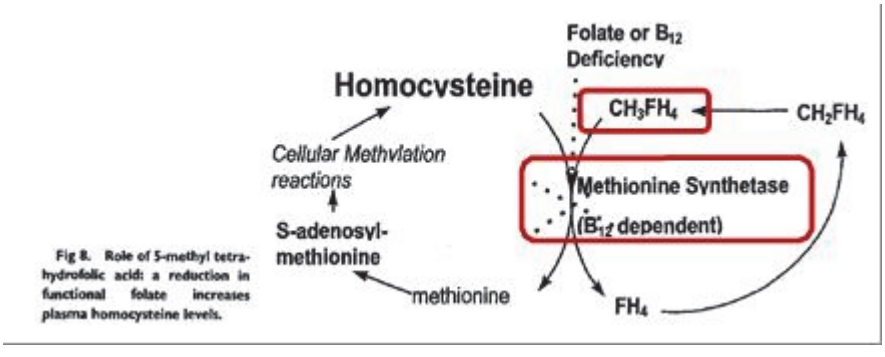

Fig 8. Role of 5-methyl tetrahydrofolic acid: a reduction in functional folate increases plasma homocysteine levels.

(Ex. 1014 at 9 (emphasis added).)

"Prior to June 1999, the studies showed that antifolate also raised methylmalonic acid levels along with homocysteine levels." (Ex. 1025 ¶ 78.) In fact, as early as 1990, it was well known that elevated MMA is linked to vitamin B12 (cobalamin) deficiency, because there are only two cobalamin dependent enzymes in vertebrates: methionine synthase, which requires methylcobalamin (vitamin B12) as a co-factor, and methylmalonyl CoA mutase. (*Id.*; Ex. 1012 at 411, Ex. 1017 at 92.) And, "methylmalonic acid and homocysteine accumulate when the two enzymatic reactions are impaired." (Ex. 1018 at 239.) The relationship between vitamin B12 and homocysteine and MMA was well known in the prior art as further explained in the figure below:

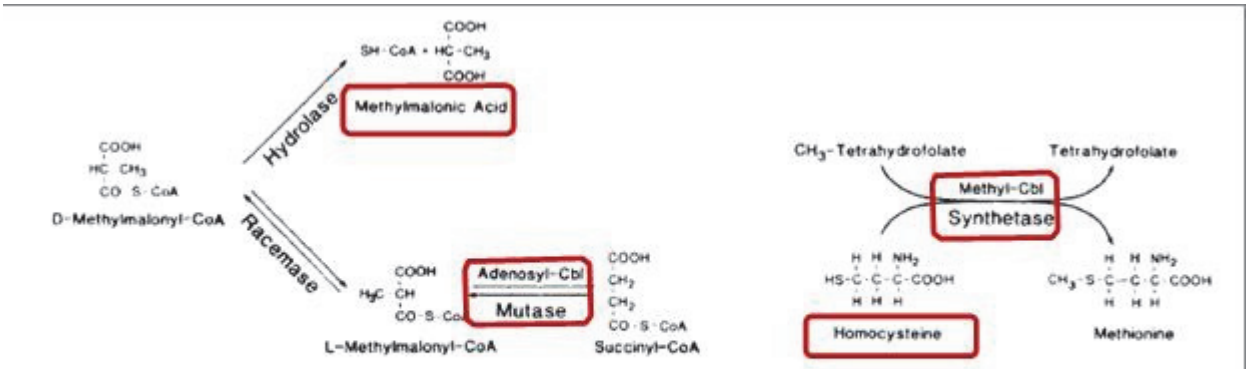

Fig. 2. L-methylmalonyl-CoA mutase (left) and methionine synthetase (right) are the two mammalian Cbl-dependent enzymes. In Cbl deficiency, L-methylmalonyl-CoA accumulates and is converted to D-methylmalonyl-CoA, which is hydrolyzed to methylmalonic acid. Homocysteine accumulates in either Cbl or folate deficiency.

(Ex. 1017 at 92 (emphasis added).)

It was also well known in the art before June 1999 that homocysteine and MMA levels need to be monitored in patients treated with antifolate. (*See e.g.*, Ex. 1008 at 126; *see also* Ex. 1017 at 93.) For example, in 1998, *Niyikiza* reported that

139 patients in a Phase II study with pemetrexed treatment were monitored for homocysteine and MMA levels, and the monitoring established that there was a strong correlation between elevated homocysteine levels and pemetrexed toxicity. (Ex. 1008 at 126–27.)

Further, a synergistic effect was shown when both vitamin B12 and folate were administered concurrently to control blood homocysteine levels. (Ex. 1010 at 11.) In addition,

> [b]ecause folate and vitamin B-12 have a synergistic function as cofactors of methionine synthase, sufficiency of both seems to be important to increase enzyme activity, whereas a higher availability of only one cofactor, especially in subjects with an already good supply of this cofactor, might lead to only a limited increase in enzyme activity.

(Ex. 1019 at 1109.)

Thus, in the case of antifolate administration, those of ordinary skill in the art would have been—**and indeed were**—"motivated to combine the antifolate administration with a combination of folic acid and vitamin B12 administration to ameliorate antifolate toxicity," with a reasonable expectation of success. (Ex. 1025 ¶ 86; *see also* Ex. 1020 at 767.) Specifically, in 1999, *Carrasco*[3] disclosed a study

[3] *Carrasco* was published in August 1999 (i.e., eleven months prior to the earliest priority application was filed (June 30, 2000)) and publicly accessible no later than

of a leukemia patient who was administered folic acid and vitamin B12 to ameliorate toxic effects caused by antifolate methotrexate treatment. (Ex. 1020 at 767–68.) In that study, the patient received folinic acid (12 mg in one single dose), folic acid (5 mg/day for 14 days) and parenteral vitamin B12 (2 mg/day for 4 consecutive days). After 10 days of treatment, the patient's "serum HCY [homocysteine] level decreased to [a] normal value (9 μmol/L)." (*Id.* at 768.)

1. Summary of the Petition's Prior Art References

a. The *'974 Patent* (Ex. 1009)

The *'974 Patent* constitutes prior art under 35 U.S.C. § 102(b) because it published when it issued in 1993. (Ex. 1009 at Cover.) The Examiner did not consider the *'974 Patent* during prosecution of the '209 Patent. (See Ex. 1001 References Cited.)

The *'974 Patent* discloses a method for treating GARTF tumors in mammals and reducing mammalian toxicity. (Ex. 1009 at Cover.) Specifically, the *'974*

November 1999 (Ex. 1030 ¶¶ 20–23, citing Exs. 1035-1039). *Carrasco* is 102(a) prior art to the challenged claims even if those claims are entitled to the Provisional Application's priority date. Moreover, even if PO could get behind *Carrasco's* publicly available date, *Carrasco* establishes a motivation to administer folic acid and B12 to ameliorate toxic effects caused by antifolate methotrexate treatment. *See, e.g., NPF Ltd. v. Smart Parts, Inc.*, 187 Fed. Appx. 973, 979 (Fed. Cir. 2006) (holding that even if evidence does not constitute prior art, it can still be considered as evidence of motivation to combine); *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-1338 (Fed. Cir. 2004) (same).

Patent discloses that administration of a folate binding protein ("FBP") binding agent (e.g., folic acid) with a GARTF inhibitor or other antifolate reduces the toxicity of such agent and enhances therapeutic efficacy. (*Id.*)

The *'974 Patent* teaches that "[a]ny GAR-transformylase inhibitor or other antifolate that binds at less than about 500 ng/ml can be utilized in the method of this invention." (*Id.* at 4:15–17.) The *'974 Patent* also teaches that pretreatment with folic acid "from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the GAR-transformylase inhibitor or other antifolate." (*Id.* at 6:22–29.) The *'974 Patent* further teaches that multiple doses of oral administration of folic acid "up to weeks before treatment with the active agent [] [will] ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment." (*Id.* at 6:32–37.) The *'974 Patent* further discloses that "about 1 mg to about 5 mg of folic acid is administered orally to a mammal about 1 to about 24 hours prior to the parenteral administration of the amount of lomotrexol which is normally required to attain the desired therapeutic benefit." (*Id.* at 6:38–42.) It additionally discloses that "[a]lthough greater or additional doses of folic acid or another FBP binding agent are also operable, the above parameters will usually bind the folate binding protein in an amount sufficient to reduce the toxicity effects normally seen upon lomotrexol administration above." (*Id.* at 6:42–47.)

b. *EP 005* (Ex. 1010)

The *EP 005* Patent Application constitutes prior art under 35 U.S.C. § 102(b) because it was published by the European Patent Office on May 4, 1994. (Ex. 1010 at Cover.) The Examiner did not consider *EP 005* during prosecution of the '209 Patent. (*See* Ex. 1001 References Cited.)

EP 005 discloses pharmaceutical preparations containing vitamin B6, folic acid, and vitamin B12 for "lowering levels of homocysteine or for the prophylaxis or for treatment of elevated levels of homocysteine" caused by "any known cause, including … [d]rugs which induce elevated homocysteine levels includ[ing] … methotrexate … and many others." (Ex. 1010 at 2, 4.) Specifically, *EP 005* discloses several "[e]xamples of … situations in which blood homocysteine levels may be elevated[, including] … cancers." (*Id.* at 9)

Further, *EP 005* acknowledges that vitamin B6, folate, and vitamin B12 deficiencies elevate homocysteine levels, and "[v]itamin B12 may be used in the form of cyanocobalamin or hydroxycobalamin or both." (*Id.* at 6, 20.) *EP 005* also discloses:

> [S]ynergism exists when vitamin B12, folate and PL [pyridoxal] are given concurrently …. [B]oth vitamin B12 and folate stimulate processes which do not lead to a reduction of the body's methionine pool but mere recycling. The resultant methionine remains available for reconversion into homocysteine.

(*Id.* at 11.)

EP 005 further discloses various methods for administering vitamin B6, folic acid, and vitamin B12 to patients. (*Id.* at 5.) For example, *EP 005* discloses that "the preparation may be formulated for parenteral administration, preferably by infusion or by intramuscular injection," and oral administration. (*Id.*) It further provides approximate daily dosages for administration. (*Id.*) *EP 005* also teaches that "the dosage regimen is time programmed, providing for different dosage rates during different periods of a course of treatment." (*Id.* at 20.)

c. *Niyikiza* (Ex. 1008)

Niyikiza constitutes prior art under 35 U.S.C. § 102(b) because it was published and accessible by January 1999 (Ex. 1030 ¶¶ 16–19) in the *Annals of Oncology*, Supplement 4 to Volume 9, in October 1998. (Ex. 1008 at 126.) The Examiner did not consider *Niyikiza* during prosecution of the '209 Patent. (*See* Ex. 1001 References Cited.)

Niyikiza describes a meta-analysis of a Phase II study of 139 patients treated with pemetrexed (MTA). (Ex. 1008 at 126.) In particular, it discloses a meta-analysis of a Phase II study assessing the relationship between toxicity following treatment with MTA and vitamin metabolites, drug exposure, and other patient baseline characteristics. (*Id.*) In this study, the patients were monitored for vitamin metabolite profiles, including homocysteine and MMA. (*Id.*)

Niyikiza discloses that a significant correlation exists between pemetrexed toxicity and increased homocysteine levels in patients treated with pemetrexed. (*Id*. at 127.) For example, *Niyikiza* discloses that "[t]oxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥ 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA." (*Id.*)

In addition, *Niyikiza* discloses that "[f]urther studies are underway in patients with renal impairment or patients who received prior cisplatin." (*Id.*)

E. Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") in oncology as of June 30, 1999—the earliest possible priority date for the '209 Patent—would be "a medical doctor with an M.D. degree who has significant experience in treating cancer patients, and a significant understanding of antineoplastic agents, including antifolates and their efficacies, safety, adverse effects, etc." (Ex. 1025 ¶ 20.) "A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others on the team, to solve a given problem. For example, an expert in nutrition, an expert in hematology, a basic scientist with expertise in biochemistry, and a clinician may be part of the team." (*Id.* ¶ 21; *see also* Ex. 1028 at 9.)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: Claims 1–22 of U.S. Patent No. 7,772,209 are obvious under 35 U.S.C. § 103(a) over *Niyikiza* in view of the *'974 Patent* and in further view of *EP 005* and the knowledge of one of ordinary skill in the art.

1. Independent Claims 1 and 12 are obvious over *Niyikiza* in view of the *'974 Patent* and in further view of EP 005 and the knowledge of one of ordinary skill in the art.

One of ordinary skill in the art prior to June 30, 1999, when seeking to treat patients with pemetrexed—an antifolate known to cause severe side effects—would first look to *Niyikiza* for guidance on "administering pemetrexed disodium" to cancer patients with minimal toxicity, and would garner from it recommendations for "administering pemetrexed disodium to a patient in need thereof," as the **Claim 1** preamble requires. (Ex. 1008 at 126.) *Niyikiza* is a printed publication in a medical journal on the precise topic of oncology, and therefore, "would be a natural starting point for an oncologist to review." (Ex. 1025 ¶ 110.) *Niyikiza* discloses a meta-analysis of a Phase II study with MTA (pemetrexed disodium) in a variety of tumors. (Ex. 1008 at 126.) From this *Niyikiza* disclosure, a POSA would understand how to practice it at the time of publication "without undue experimentation, in view of the nature of the methods and the state of the art" available at the time of the invention. (Ex. 1025 ¶ 112.) *See In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1380 (Fed. Cir. 2007) ("One skilled in the art

would naturally look to prior art addressing the same problem as the invention at hand, and in this case would find an appropriate solution.").

With respect to **Claim 1** of the '209 Patent, a POSA would understand from *Niyikiza* the desirability, when treating patients with pemetrexed disodium, of reducing pemetrexed-associated toxicity by "administering an effective amount of folic acid," as **Claim 1(a)**[4] requires, "an effective amount of methylmalonic acid lowering agent," as **Claim 1(b)** requires, "administering an effective amount of pemetrexed disodium," as **Claim 1(c)** requires, and "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," as **Claim 1(d)** requires, as described below. (Ex. 1001 at 10:56–65; Ex. 1025 ¶¶ 111, 113–14.)

Specifically, *Niyikiza* teaches "administering pemetrexed disodium" to a patient, as required by the Claim 1 preamble and Claim 1(c). (Ex. 1008 at 126; Ex. 1025 ¶ 111.) *Niyikiza* also teaches:

> Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast,

[4] Claim 1 is divided into elements for ease of explanation.

> pancreas, and esophagus at baseline and once each cycle thereafter. … Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (> 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA.

(Ex. 1008 at 126–27.) Armed with this *Niyikiza* disclosure—that MTA-induced elevated levels of homocysteine following MTA treatment cause severe toxicities—an ordinarily skilled artisan "would look for ways to reduce homocysteine levels" to reduce pemetrexed toxicity. (Ex. 1025 ¶ 114.) Thus, a POSA "would have been motivated to look to published methods disclosed in the *'974 Patent* and *EP 005* to lower elevated homocysteine levels to reduce pemetrexed toxicity." (*Id.*; see also Ex. 1001 at 2:29–31.) *See Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 977 (Fed. Cir. 2014) ("When a claimed invention involves a combination of elements, however, any need or problem known in the relevant field of endeavor at the time of invention can provide a reason to combine.").

Both *'974 Patent* and *EP 005* teach that "administering an effective amount of folic acid," as required by **Claim 1(a)**, to a patient would reduce antifolate toxicity caused by elevated plasma homocysteine levels. (Ex. 1001 at 10:57–58.) For example, the *'974 Patent* teaches that "the toxic effects of ... related GAR-

transformylase inhibitors [e.g., pemetrexed] and other antifolate agents which bind to folate binding protein (FBP) ... can be significantly reduced by the presence of a FBP binding agent [folic acid], without adversely affecting therapeutic efficacy." (Ex. 1009 at 1:46–53 (emphasis added).) Similarly, *EP 005* teaches "[a] pharmaceutical preparation which comprises in combination, each in a concentration and form effective to suppress homocysteine levels in plasma … b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo…." (Ex. 1010 at 19 (emphasis added).) From these *'974 Patent* and *EP 005* teachings, "a POSA would have understood that to reduce the toxic effects of pemetrexed treatment—to lower elevated levels of plasma homocysteine—'an effective amount of folic acid would be administered' to a patient, as required by **Claim 1(a)**." (Ex. 1025 ¶ 118.) Therefore, because a POSA administering pemetrexed would seek to avoid the toxic effects of the drug, it would have been obvious to administer folic acid to the patient to reduce pemetrexed toxicity. (*Id.* ¶ 119.) Further, "a POSA would administer an effective amount of folic acid based on the clinical condition of the patient, without undue experimentation." (*Id.*)

With respect to **Claim 1(b)**—"an effective amount of a methylmalonic acid lowering agent"—a POSA would understand from *Niyikiza* that homocysteine and MMA levels should be measured in cancer patients at the beginning and during pemetrexed treatment to assess the toxicity of the drug. (Ex. 1001 at 58–59; Ex.

1025 ¶ 120.) As described above, a POSA "would have been motivated to look to published methods disclosed in the *'974 Patent* and *EP 005* and would have administered folic acid to lower homocysteine levels to reduce pemetrexed toxicity." (Ex. 1025 ¶ 114.) In addition, upon reading *Niyikiza*, a POSA would have also administered "a methylmalonic acid lowering agent," as described above, in order to lower MMA levels, elevated homocysteine levels, and to reduce pemetrexed toxicity. (*Id.* ¶ 121.) A POSA at the time of the invention would have known that vitamin B12 would lower MMA levels. (*Id.*) Further, *EP 005* teaches that administering vitamin B12 in combination with folic acid would reduce homocysteine levels. (Ex. 1010 at 2.) For example, *EP 005* discloses that "an unexpected synergism exists when vitamin B12, folate … are given concurrently." (*Id.* at 11.)

Further, by 1999, it was obvious to a POSA that MMA lowering agent, such as vitamin B12, should be administered along with folic acid to reduce homocysteine levels. (Ex. 1025 ¶ 121, and ¶¶ 86-87, 178 (citing Ex. 1020).) A POSA would have understood from the art available at the time of the invention that remethylation of homocysteine to methionine would require both folic acid and MMA lowering agent, such as vitamin B12. (Ex. 1010 at 2; Ex. 1025 ¶¶ 121, 124.) For example, the prior art reference *Refsum* discloses:

> [T]he intracellular homocysteine is either salvage to methionine through remethylation, or conversion to cysteine via the trans-sulfuration pathway. In most tissues, the former reaction is catalysed by the ubiquitous enzyme methionine synthase which requires vitamin B12 as a cofactor and 5-methyltetrahydrofolate as methyl donor; thus 5-methyltetrahydrofolate enters the pool of reduced folates, and homocysteine is remethylated to methionine. … Measurement of plasma homocysteine is therefore a promising laboratory test for evaluating cobalamin or folate deficiency states. It may be particularly useful when used in conjunction with serum methylmalonic acid, which is a specific measure of disturbances of cobalamin metabolism.

(Ex. 1012 at 411–12; Ex. 1025 ¶ 125.)

Similarly, the prior art reference *Allen* teaches that the "measurement of both serum methylmalonic acid and total homocysteine is often required for the optimal diagnosis of Cbl [cobalamin] deficiency." (Ex. 1017 at 93.) Thus, "a POSA would have understood from the art that administering folic acid alone would result in vitamin B12 deficiency because remethylation of homocysteine requires both folic acid and vitamin B12, and that vitamin B12 deficiency would raise methylmalonic acid levels." (Ex. 1025 ¶ 127.) Thus, because a POSA treating a patient with pemetrexed would seek to ameliorate pemetrexed toxicity, it would have been obvious to administer an effective amount of MMA lowering agent, as **Claim 1(b)** requires, and such agent must be selected from vitamin B12 or its derivatives, as **Claim 1(d)** requires. (Ex. 1010 at 2, 6, 12, 20; Ex. 1025 ¶ 128.) *See In re Preda*,

401 F.2d 825, 826 (CCPA 1968) ("it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom"); *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (element considered disclosed in a prior art reference if it is "within the knowledge of a skilled artisan").

Independent claim, **Claim 12** of the '209 Patent, "is written in Jepson format, meaning that the claim first describes the scope of the prior art and then claims an improvement over the prior art." *Dow Chem. Co. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1368 (Fed. Cir. 2001). Specifically, the Claim 12 preamble recites:

> An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

(Ex. 1001 at 11:26–28 (emphasis added).) Because "a preamble is impliedly admitted to be prior art when a Jepson claim is used," the patentee has admitted that the Claim 12 preamble is prior art, rather than a point of novelty. *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 315 (Fed. Cir. 1985); *see In re Glatt Air Techniques, Inc.*, 630 F.3d 1026, 1028 (Fed. Cir. 2011) (rejecting a claim "as obvious in view of the admitted prior art from the claim preamble and a single cited reference").

An ordinarily skilled artisan seeking to treat cancer patients with pemetrexed disodium as in **Claim 12's preamble**, "would look to *Niyikiza* for guidance on 'administering pemetrexed disodium to a patient in need of chemotherapeutic treatment,'" as the preamble requires. (Ex. 1025 ¶ 129; Ex. 1008 at 126.) *See In re Icon Health & Fitness, Inc.*, 496 F.3d at 1380.

With respect to **Claim 12** of the '209 Patent, a POSA would understand from *Niyikiza* the desirability, when treating patients with pemetrexed disodium, of reducing pemetrexed-associated toxicity by "administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium," as **Claim 12(a)** requires, "administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium," as **Claim 12(b)** requires, and "administration of pemetrexed disodium," as **Claim 12(c)** requires, as described below. (Ex. 1001 at 11:29–12:4; Ex. 1025 ¶ 130.)

Specifically, as explained above, *Niyikiza* teaches "administration of pemetrexed disodium," as **Claim 12(c)** requires, and elevated homocysteine levels following pemetrexed treatment. (Ex. 1008 at 126–27.)

With respect to **Claim 12(a)**—"administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium"—a POSA would understand from *Niyikiza*, as explained above, that homocysteine levels should be lowered in order to ameliorate pemetrexed toxicity

"[b]ecause *Niyikiza* published a meta-analysis of a phase II study of pemetrexed showing elevated levels of homocysteine as an indicator for pemetrexed toxicity." (Ex. 1025 ¶ 131.) Further, a POSA would have understood from the art available at the time of the invention that cancer would elevate homocysteine levels in a patient. (*See id.* ¶ 132.) For example, *EP 005* discloses that cancers and antifolate methotrexate elevate "blood homocysteine levels." (Ex. 1010 at 4, 9.)

Armed with these prior art disclosures, a POSA would have been motivated to lower pretreatment homocysteine levels in cancer patients before starting pemetrexed therapy, and would look to the pretreatment method disclosed in the *'974 Patent* and *EP 005*, and the dosage regimen disclosed in *EP 005*. (Ex. 1025 ¶ 133.) *See Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197 (2014) ("[T]he motivation to combine does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a person of skill in the art at the time of invention"); *see also Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d at 977; *Rogers v. Desa Int'l, Inc.*, 198 Fed. Appx. 918, 922 (Fed. Cir. 2006) ("Evidence that those of ordinary skill in the art in fact combined the prior art teachings as claimed is certainly evidence that they were motivated to do so. Such evidence shows the knowledge of the skilled artisan at the time of the invention, which can provide the basis for a motivation to combine.").

The *'974 Patent* discloses pretreatment with folic acid before the antifolate therapy. (Ex. 1009 at 6:22–47; Ex. 1025 ¶ 134.) For example, the *'974 Patent* teaches that "1 mg to about 5 mg of folic acid is administered orally to a mammal about 1 to about 24 hours prior to the parenteral administration of the amount of lomotrexol [antifolate]…." (Ex. 1009 at 6:37–47 (emphasis added).) Although the *'974 Patent* does not explicitly teach 'administration of between about 350 μg and about 1000 μg of folic acid prior to administration of pemetrexed disodium,' as Claim 12(a) requires, the *'974 Patent*'s administration of 1 mg to about 5 mg of folic acid overlaps the claimed dosage range. (Ex. 1025 ¶ 134.) *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("'[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'") (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).

Like the *'974 Patent*, which discloses pretreatment with folic acid before antifolate therapy, *EP 005* discloses "pharmaceutical preparations [containing folate] for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in patients and for counteracting the harmful effects associated with homocysteine." (Ex. 1010 at 2, 20 (emphasis added).) *EP 005* also discloses that "the dosage regimen is time programmed, providing for different dosage rates during different periods of a course of [antifolate]

treatment." (*Id.* at 6, 20 (emphasis added).) *EP 005* further discloses the dosage regimen and "approximate daily dosages as (µg/d/kg body weight).

	a) Vitamin B6	b) Folic Acid	c) Vitamin B12
Broadest range	15-750	1,5-150	1,5-75
preferred range	30-400	7,5-50	3-15
more preferred range	75-250	10-30	7-10
typical example	150	15	7,5

These dosages may be exceeded somewhat for short durations, e.g. at the beginning of the treatment." (*Id.* at 5, 19.) *EP 005* also discloses:

> The following quantities refer to one daily dose for an adult patient of approximately 70kg body weight. (PL=pyridoxal; Fol=folate; B12=Vitamin B12) Quantities are given in milligrams per day.

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.)

From these *EP 005* disclosures, it would have been obvious to a POSA that *EP 005*'s folic acid dosage ranges encompass the dosage range recited in **Claim**

12(a). (Ex. 1025 ¶¶ 135–39.) *See In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003) ("[W]hen, as here, the claimed ranges are completely encompassed by the prior art, the [obviousness] conclusion is even more compelling than in cases of mere overlap.").

From these prior art disclosures, as described above, "a POSA would have been motivated to combine the *'974 Patent*'s disclosure—'pretreatment with folic acid'—with *EP 005's* disclosure—dosage range of folic acid—and would have arrived at—'administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium,' as **Claim 12(a)** requires." (Ex. 1025 ¶ 140.)

With respect to **Claim 12(b)**—"administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium"—a POSA would understand from *EP 005* that a patient would be treated with about 500 μg to about 1500 μg of vitamin B12 prior to the pemetrexed treatment. (Ex. 1010 at 2, 5, 8, 19, 20; Ex. 1025 ¶ 141.) Because *EP 005* discloses that the "pharmaceutical preparations [containing vitamin B12] for … the prophylaxis or treatment of elevated levels of homocysteine in patients," "it would have been obvious to a POSA that *EP 005* discloses pretreatment with vitamin B12 before pemetrexed treatment." (Ex. 1010 at 2, 4; Ex. 1025 ¶ 141.) "Moreover, it would have been obvious to a POSA that homocysteine levels must be normalized

prior to the pemetrexed treatment to ameliorate pemetrexed toxicity," because *EP 005* discloses that "[e]xamples of … situations in which blood homocysteine levels may be elevated[, including] … cancers," and "folate antagonistic drug [e.g., pemetrexed], which has tendency to raise homocysteine levels." (Ex. 1010 at 9 (emphasis added); Ex. 1025 ¶ 142.)

As described above, a POSA would have understood from the art at the time of the '209 Patent that cancer and antifolate treatment would cause elevated levels of plasma homocysteine. (Ex. 1025 ¶ 143; *see also* Ex. 1012 at 411, 412.) Thus, "it would have been obvious to a POSA to reduce cancer-induced homocysteine levels prior to pemetrexed treatment by administering folic acid and vitamin B12, in order to reduce pemetrexed toxicity in cancer patients." (Ex. 1025 ¶ 143, and ¶¶ 86-87, 178 (citing Ex. 1020).) Also, *EP 005* discloses that "[r]egarding the treatment and prophylaxis of hyperhomocysteineaemia [elevated homocysteine levels], it is known that … vitamin B12 and folate play a role in regulating the methionine - homocysteine pathway and controlling levels of homocysteine …." (Ex. 1010 at 3.) Further, "a POSA would understand that the pretreatment with folic acid and vitamin B12 would lead to better compliance" with the treatment and "a better therapeutic effect of pemetrexed treatment because a patient would be more likely to follow the pemetrexed regimen due to the lessened side effects resulting from the folic acid and vitamin B12 pretreatment." (Ex. 1025 ¶ 144.)

Moreover, *EP 005* discloses that an unexpected synergism exists when vitamin B12, folate … are given concurrently." (Ex. 1010 at 11 (emphasis added).) Additionally, "it would have been obvious to a POSA that administering folic acid alone would not result in complete remethylation of homocysteine to methionine because methionine synthase requires both folic acid, as a methyl group donor, and vitamin B12, as a co-factor, to catalyze that remethylation reaction." (Ex. 1025 ¶ 145; *see also* Ex. 1010 at 2; Ex. 1012 at 412.) Also, it was well known in the art at the time of the '209 Patent that "administering folic acid alone would ameliorate the early symptoms of vitamin B12 deficiency without treating the underlying condition, leading to irreversible nerve damage." (Ex. 1025 ¶ 143.) Thus, a POSA seeking to ameliorate pemetrexed toxicity would administer folic acid *along with* vitamin B12 prior to pemetrexed treatment. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (finding obviousness where "the skilled artisan would have had that reasonable expectation of success that [application of the prior art method] would work for its intended purpose").

Although *EP 005* does not explicitly disclose the specific timing or duration of treatment recited in the '209 Patent claims, the '209 Patent correctly states that the amount of folic acid and vitamin B12 that is actually administered "will be determined by a physician, in light of the relevant circumstances…." (Ex. 1001 at 5:37–41.) Therefore, by 1999, "it would have been obvious to a POSA to adjust the

amount, method (i.e., oral or intramuscular administration), and duration (i.e., the length of time for which folic acid alone or in combination with vitamin B12) of administration of folic acid and vitamin B12, depending on clinical condition of the patient, without undue experimentation." (Ex. 1025 ¶ 147.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295.

Thus, "a POSA would have been highly motivated to combine *Niyikiza*"—"which teaches that pemetrexed toxicity correlates with elevated levels of homocysteine"—with the *'974 Patent*—"which teaches pretreatment with folic acid"— and with *EP 005*—"which teaches that administration of folic acid and vitamin B12 in dosage ranges, that encompass claimed dosage ranges, lowers elevated homocysteine levels caused by antifolate treatment," rendering Claim 12 obvious. (Ex. 1025 ¶ 148.) *See Bayer Schering Pharma AG v. Barr Labs., Inc., 575* F.3d 1341, 1347 (Fed. Cir. 2009) ("'When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.'") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

2. Dependent Claims 2–10 and 14–21 are obvious.

Claims 2–10 depend from Claim 1, and Claims 14–21 depend from Claim 12. These dependent claims merely add limitations already known in the field and obvious to one of ordinary skill in the art. **Claim 2** requires that "the methylmalonic acid lowering agent is vitamin B12," while **Claims 3 and 14** require that "vitamin B12 is administered as an intramuscular injection of about 500 μg to about 1500 μg," **Claims 4 and 15** require that "vitamin B12 is administered as an intramuscular injection of about 1000 μg," **Claims 5 and 21** require that "the vitamin B12 administration is repeated about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued," **Claims 6 and 19** require that "folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium," **Claims 7 and 20** require that "folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium," **Claims 8 and 16** require that "between 0.3 mg to about 5 mg of folic acid is administered orally," **Claims 9 and 17** require that "about 350 μg to about 1000 μg of folic acid is administered," and **Claims 10 and 18** require that "350 μg to 600 μg of folic acid is administered." (Ex. 1001 at 10:66–11:22, 12:7–27 (emphasis added).)

Niyikiza teaches:

> Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. … Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥ 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA.

(Ex. 1008 at 126–27.) Thus, upon reading *Niyikiza*, in view of the art available at the time of the alleged '209 invention, as described above, it would have been obvious to a POSA to administer "a methylmalonic acid lowering agent" in order to lower MMA levels to ameliorate pemetrexed toxicity, and to look for published methods to find MMA lowering agent. (Ex. 1025 ¶¶ 120–21, 124–27.)

Additionally, *EP 005* discloses that "an unexpected synergism exists when vitamin B12, folate … are given concurrently." (Ex. 1010 at 11.) Although, *EP 005* does not explicitly disclose that vitamin B12 is a MMA lowering agent, it discloses that administering vitamin B12 in combination with folic acid would reduce homocysteine levels. (*Id.* at 2, 4.) For example, *EP 005* discloses that "pharmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising: … b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo, c) vitamin B12 ...." (*Id.* at 1.) As explained above with respect to Claim 1, because it was within the knowledge of a POSA

that vitamin B12 is known to lower MMA levels in the body, it would have been obvious to a POSA that "the methylmalonic acid lowering agent is vitamin B12," as in **Claim 2**. (Ex. 1025 ¶ 149.)

In addition to administering vitamin B12 as the MMA lowering agent described above, *EP 005* further discloses administering various dosages of vitamin B12 by intramuscular injection. For example, *EP 005* discloses that "pharmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising: … c) vitamin B12," "[t]he preparation may be galenically formulated for parenteral administration, preferably by infusion or by intramuscular injection," and "[t]he preparations … are formulated to provide approximate daily dosages as follows (µg/d/kg body weight).

	a) Vitamin B6	b) Folic Acid	c) Vitamin B12
Broadest range	15-750	1,5-150	1,5-75
preferred range	30-400	7,5-50	3-15
more preferred range	75-250	10-30	7-10
typical example	150	15	7,5

(Ex. 1010 at 1, 5, 19 (emphasis added.)

EP 005 also discloses (at page 8):

> The following quantities refer to one daily dose for an adult patient of approximately 70kg body weight. (PL=pyridoxal; Fol=folate; B12=Vitamin B12) Quantities are given in milligrams per day.

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

These teachings meet "the vitamin B12 is administered as an intramuscular injection of about 500 μg to about 1500 μg" requirement of **Claims 3 and 14**, and "vitamin B12 is administered as an intramuscular injection of about 1000 μg" requirement of **Claims 4 and 15** because the dosage ranges disclosed in *EP 005* encompass the claimed dosage ranges. (Ex. 1025 ¶¶ 150–51.) *See In re Peterson*, 315 F.3d at 1329–30.

Additionally, because *EP 005* teaches that "the preparation is formulated to make available to the patient … an effective dosage of the vitamin B12," "the preparation may be … by intramuscular injection … inherently provides for a retarded availability of the ingredients," and "the dosage regimen is time programmed, providing for different dosage rates during different periods of a course of treatment," "it would have been obvious to a POSA that the dosage and

time program would be adjusted according to the clinical condition of a patient." (Ex. 1010 at 5, 19, 20 (emphasis added); Ex. 1025 ¶ 152.) The '209 Patent states:

> [I]t will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

(Ex. 1001 at 5:37–50.) Thus, the above *EP 005* teachings, in view of POSA's knowledge, render **Claims 5 and 21**—requiring "the vitamin B12 administration is repeated about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued"—obvious. (Ex. 1025 ¶ 154.) *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012) (finding substantial question of validity because, "'[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability'") (quoting *KSR*, 550 U.S. at 417).

Additionally, the *'974 Patent* discloses administering folic acid prior to antifolate treatment. For example, the *'974 Patent* discloses:

> The FBP binding agent [folic acid] is administered to the subject mammal prior to treatment with the GAR-transformylase inhibitor [e.g., pemetrexed] or other antifolate … multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent….

(Ex. 1009 at 6:22–36 (emphasis added).) Although the *'974 Patent* does not explicitly disclose pemetrexed, as described above and known to a POSA, pemetrexed is a GAR-transformylase inhibitor. (Ex. 1025 ¶¶ 156, 157.)

Like the *'974 Patent*, which teaches pretreatment with folic acid, *EP 005* discloses a dosage regimen for prophylactic treatment of elevated homocysteine levels, as explained above with respect to Claim 12(a). (*See* Ex. 1010 at 5.) For example, *EP 005* discloses that "[p]harmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising: … b) folate or a suitable active metabolite of folate," "pharmaceutical preparations for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in patients," and "the dosage regimen is time programmed, providing for different dosage rates during different periods of a course of treatment." (*Id.* at 1, 4, 20 (emphasis added).) Upon reading these *'974 Patent* and *EP 005* disclosures, it would have been obvious to a POSA to administer folic acid "1 to 3 weeks" prior to pemetrexed treatment, as required by **Claim 6 and 19**. (Ex. 1025 ¶¶ 158–59.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295.

The *'974 Patent* also discloses that "[p]retreatment with the suitable amount of FBP binding agent [folic acid] from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the GAR-transformylase inhibitor [e.g., pemetrexed] or other antifolate" and renders **Claims 7 and 20**—requiring "folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium"—obvious. (Ex. 1009 at 6:24–29 (emphasis added); Ex. 1025 ¶ 160.)

The *'974 Patent* further teaches that "1 mg to about 5 mg of folic acid is administered orally to a mammal…." (Ex. 1009 at 6:38–47 (emphasis added).) Similarly, *EP 005* discloses oral administration of various dosages of folic acid. For example, *EP 005* discloses that "the preparation … preferably designed for oral administration," "a sub-linqual tablet … is produced in such a manner that the PL, vitamin B12 and folate components … formulated to contain all or any one of the three vitamins," "the preparations in accordance with the invention are formulated to provide approximate daily dosages as follows (µg/d/kg body weight),"

	a) Vitamin B6	b) Folic Acid	c) Vitamin B12
Broadest range	15-750	1,5-150	1,5-75
preferred range	30-400	7,5-50	3-15
more preferred range	75-250	10-30	7-10
typical example	150	15	7,5

"[t]hese dosages may be exceeded somewhat for short durations, e.g. at the beginning of the treatment," and "gelatine capsules, filled with a granulate, formulated for timed release (over about 8 hours) in a manner known per se, contained per capsule:"

Pyridoxine	10 mg
thiamine	3 mg
riboflavine	4 mg
nicotinamide	20 mg
cyanocobalamine	50 µg
ascorbic acid	200 mg
folic acid	1 mg
calcium panthothenate	10 mg.

The preparation according to the invention was formulated as follows (per oral dosage unit):-

a)	(i) (ii)	pyridoxal pyridoxine	2 mg 8 mg; (i) + (ii) = 10 mg
b) c)		folate cyanocobalamin	0,65 mg 0,4 mg.

(Ex. 1010 at 5, 11, 14, 15, 17, 19 (emphasis added).)

EP 005 also discloses:

The following quantities refer to one daily dose for an adult patient of approximately 70kg body weight. (PL=pyridoxal; Fol=folate; B12=Vitamin B12) Quantities are given in milligrams per day.

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.)

From these *'974 Patent* and EP 005 disclosures, "it would have been obvious to a POSA that folic acid would be administered orally 'between 0.3 mg to about 5 mg,' as required by **Claims 8 and 16**, because both references teach oral administration of folic acid, and the dosage ranges disclosed in the both references encompass claimed folic acid dosages." (Ex. 1025 ¶ 162.) *See In re Peterson*, 315 F.3d at 1329–30. It would have been further obvious to a POSA to administer "about 350 μg to about 1000 μg of folic acid," as **Claims 9 and 17** require, and "350 μg to 600 μg of folic acid," as **Claims 10 and 18** require, because, as described above, *EP 005* discloses these dosage ranges. (Ex. 1025 ¶ 163.) *See In re Peterson*, 315 F.3d at 1329–30.

3. Dependent Claims 11, 13, and 22 are obvious.

Claim 11 depends from Claim 1, and Claims 13 and 22 depend from Claim 12. These dependent claims merely add limitations already known in the field and obvious to one of ordinary skill in the art. Specifically, **Claims 11, 13, and 22** require "administration of cisplatin to the patient," and Claim 12 elements requiring "administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium," "administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium," and "administration of pemetrexed disodium" are incorporated in the first parts of Claims 13 and 22. (Ex. 1001 at 11:23–24, 11:28–30, 12:1–3, 12:5–6, 12:28–29 (emphasis added).)

As described above, "*Niyikiza* teaches administering pemetrexed to a patient in need thereof, while the *'974 Patent* teaches administering folic acid and *EP 005* teaches administering folic acid and vitamin B12 in combination with antifolate to a patient." (Ex. 1025 ¶ 164.) Also, as described above, both the *'974 Patent* and *EP 005* teach pretreatment with folic acid, while *EP 005* teaches pretreatment with vitamin B12, as the first parts of **Claims 13 and 22** require. (*Id.* ¶ 165.)

Additionally, *Niyikiza* discloses administering cisplatin to a patient. For example, *Niyikiza* discloses that "[f]urther studies are underway in patients … who received prior cisplatin." (Ex. 1008 at 127 (emphasis added).) Thus, *Niyikiza*'s

teaching meets "administration of cisplatin to the patient" requirement of **Claims 11, 13, and 22** and renders these claims obvious to one of ordinary skill in the art. (Ex. 1025 ¶ 166.)

In sum, "in view of administering pemetrexed disodium to Phase II cancer patients taught by *Niyikiza*, it would have been obvious to a POSA to implement the administration of an effective amount of folic acid and vitamin B12 disclosed in the *'974 Patent* and *EP 005* to reduce pemetrexed toxicity." (*Id.* ¶ 167.) *See Abbott Labs v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006) (finding substantial question of invalidity because the combination of references for "the reduction of systemic side effects would not be surprising and would not be unexpected."). Therefore, a POSA "treating a patient with pemetrexed (and cisplatin) in accordance with the disclosures in *Niyikiza* would look to published methods for lowering elevated levels of homocysteine levels caused by cancer and pemetrexed treatment—such as folic acid administration and pretreatment with folic acid found in the *'974 Patent* and dosages, methods, and duration of folic acid and vitamin B12 administration prior to or during pemetrexed treatment taught by *EP 005*—and would view Claims 1-22 of the '209 Patent obvious in view of these three references." (*Id.* ¶ 168.) *See Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) ("The motivation need not be found in the references sought to be combined, but may be found in any number of sources,

including common knowledge, the prior art as a whole, or the nature of the problem itself.")

For these reasons, "it would have been obvious to a POSA to combine *Niyikiza* teaching with those of *'974 Patent* and *EP 005* to arrive at the alleged invention claimed in the '209 Patent." (*Id.* ¶ 169.) *See KSR Int'l Co.*, 127 S. Ct. at 1731.

B. The S.D. of Indiana Decision Finding that Teva Did Not Establish by Clear and Convincing Evidence that Certain Claims of the '209 Patent are Obvious is Not Relevant to this Proceeding.

Although the District Court for the Southern District of Indiana has previously addressed the validity of the '209 Patent, it did so by addressing portions of the prior art from Wockhardt's Ground 1 in a different context than as used in Wockhardt's Ground 1. *See 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"); *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1429, fn. 3 (Fed. Cir. 1988) ("'A patent is not held valid for all purposes but, rather, not invalid on the record before the court'" and "'simply remains valid until another challenger carries'" the burden of showing invalidity.); *In re Cipro Cases I & II*, 61 Cal. 4th 116, 143 (Cal. 2015) ("Each case may show only that a patent has not been invalidated, yet.").

Wockhardt contends that Claims 1–22 of the '209 Patent are obvious under 35 U.S.C. § 103(a) over *Niyikiza*[5] in view of the *'974 Patent* and in further view of *EP 005* and the knowledge of one of ordinary skill in the art. Specifically,

[5] Although the District Court briefly addresses the *Niyikiza* reference, it does so by addressing multiple *Niyikiza* references, and even testimony from *Niyikiza* regarding studies that took place after the '209 Patent's priority date. The District Court then went on to conclude, by generally referencing multiple of these *Niyikiza* references, that Dr. Niyikiza found "that there was no statistical correlation between toxicity and the other variable he measured, including MMA, suggesting at the time that there was no correlation between toxicity and patients' vitamin B_{12} levels." (Ex. 1028 at 7.) The *Niyikiza* reference upon which Wockhardt relies contains no such findings regarding MMA, nor does any other *Niyikiza* reference that Wockhardt can locate. Thus, this District Court finding has no bearing on the Wockhardt's Ground 1 reliance on a *Niyikiza* reference that merely mentions that "Homocystein (Hcys), cystathionine and methylmalonic acid [MMA] were measured," and that the "[p]rognostic factors considered were age, gender, prior treatment, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC," but then does not include results or conclusions for the majority of the factors measured or considered, including MMA. (Ex. 1008 at 126–27.)

Wockhardt asserts that, based on *Niyikiza*'s disclosure—that MTA-induced elevated levels of homocysteine following MTA treatment cause severe toxicities—an ordinarily skilled artisan would look for ways to reduce a patient's homocysteine levels to reduce pemetrexed toxicity. Thus, because of *Niyikiza*'s disclosure, a POSA would have been motivated to look to previously-published methods for lowering a patient's homocysteine levels, including those disclosed in the *'974 Patent* and *EP 005*. *See Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968 (Fed. Cir. 2014) ("When a claimed invention involves a combination of elements, however, any need or problem known in the relevant field of endeavor at the time of invention can provide a reason to combine.").

As discussed in more detail in Ground 1, the *'974 Patent* teaches that "the toxic effects of ... related GAR-transformylase inhibitors [e.g., pemetrexed] and other antifolate agents which bind to folate binding protein (FBP) ... can be significantly reduced by the presence of a FBP binding agent [folic acid], without adversely affecting therapeutic efficacy." (Ex. 1009 at 1:46–53 (emphasis added.) Because a POSA would know that pemetrexed is a GARTF inhibitor, a POSA looking to follow *Niyikiza*'s teachings to reduce pemetrexed toxicity by lowering a patient's homocysteine levels, would have a reasonable expectation that following the *'974 Patent's* methods would solve this pemetrexed toxicity challenge identified in *Niyikiza*.

In contrast to Wockhardt's argument that the '209 Patent is obvious over *Niyikiza* in light of the *'974 Patent*, the District Court looked at the *'974 Patent* without first considering *Niyikiza*, and determined that, because "pemetrexed had not even been discovered at the time the *'974 Patent* was filed," "a POSA would not have thought the *'974 Patent* was referring to pemetrexed." (Ex. 1028 at 15.) While it is true that, a POSA reading the *'974 Patent* would not have thought the *'974 Patent* was referring to pemetrexed, it is also true that a POSA having read *Niyikiza* and looking for a way to lower a pemetrexed-induced patient's homocysteine levels, would have expected the *'974 Patent's* methods—which taught applicability for all GARTF inhibitors—to be successful when applied to *Niyikiza*'s pemetrexed teachings. Thus, the District Court's factual findings related to non-obviousness regarding the *'974 Patent* alone are not applicable to this Petition's assertions of obviousness over *Niyikiza* in light of the *'974 Patent*.

Additionally, because this Petition further relies on obviousness in light of *EP 005*—which, as discussed, the District Court did not consider—the District Court's factual findings related to non-obviousness are wholly inapplicable to this Petition's assertion of obviousness over the *combination* of *Niyikiza* in light of *both* the *'974 Patent* and *EP 005*. Moreover, the District Court assumed a priority date of June 1999, and did not consider the *Carrasco* (Ex. 1020) evidence

establishing a POSA's motivation to combine folic acid and B12 to ameliorate toxic effects caused by antifolate methotrexate treatment. (Ex. 1025 ¶¶86-87, 178.)

VII. ANY SECONDARY CONSIDERATIONS ARE INSUFFICIENT TO OVERCOME THE OBVIOUSNESS OF CLAIMS 1–22.

Applicant has the burden of establishing the existence and sufficiency of any secondary considerations of non-obviousness, as well as their nexus and commensurateness with the claims. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013) ("Where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.) Although secondary considerations must be taken into account, they do not control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney, Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). And, in cases where a strong prima facie obviousness showing exists, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence may not dislodge the primary conclusion of obviousness. *See, e.g., Leapfrog Enters. Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

During prosecution, applicant argued:

> Applicants unexpectedly discovered vitamin B12 and folic acid as claimed reduces toxicity of pemetrexed disodium. … Under the Supreme Court's decision in KSR, the combination of a methylmalonic acid lowering agent, particularly vitamin B12 or a pharmaceutical derivative, and pemetrexed disodium does more than yield predictable results, the combination works together in an unexpected and fruitful manner. Therefore, the rejection is clearly improper and should be withdrawn.

(Ex. 1002 at 89–91.)

However, as explained above, "[t]here is nothing unexpected about reducing the pemetrexed toxicity with vitamin B12 and folic acid" because the prior art available at the time of the invention clearly shows that "vitamin B12 and folic acid reduce pemetrexed-induced elevated homocysteine levels, thereby reducing pemetrexed toxicity. Thus, there is no nexus between the alleged secondary considerations of unexpected discovery—'vitamin B12 and folic acid as claimed reduces toxicity of pemetrexed disodium'—and the '209 Patent claims requiring various doses of folic acid and vitamin B12 because the prior art discloses all of the elements of the '209 Patent claims." (Ex. 1025 ¶ 171.)

Additionally, during litigation, a District Court agreed with the applicant's argument during prosecution, and found that "the regimen of administering pemetrexed according to the methods that are claimed in the '209 Patent exhibited properties that would have been unexpected to the POSA in June 1999." (Ex. 1028

at 26–27.) Specifically, the Court found that "[a] POSA would have expected the regimen covered in the '209 Patent to not only reduce toxicity over unsupplemented administration of pemetrexed, but also reduce the efficacy," but that reduced efficacy did not occur. (*Id.* at 27.) However, none of the claims of the '209 Patent is directed to the efficacy of the claim treatment, such that the '209 Patent claims have no nexus to this finding of "unexpected properties," as required for a showing of secondary considerations of non-obviousness. See *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992.).

To support conclusions of unexpected results, the evidence asserted as unexpected must actually have been obtained. *See, e.g., In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1973). And the evidence must include a comparison with the closest prior art. *See, e.g., In re Merchant*, 575 F.2d 865, 869, (CCPA 1978). However, as described above, the closest prior art—*Niyikiza*, the *'974 Patent*, and *EP 005*—described all of the elements of Claims 1–22. (Ex. 1025 ¶ 169.) Thus, one of ordinary skill in the art "would not have considered administering pemetrexed in combination with vitamin B12 and folic acid to be surprising." (*Id.* ¶ 172.)

Further, applicant provides no independent data to support his unexpected result allegation that administering pemetrexed in combination with vitamin B12 and folic acid claimed in the '209 Patent would be better than prior art references.

(*See* Ex. 1001; Ex. 1025 ¶ 173.) Superiority of, or difference in results, if not shown to be unexpected, is insufficient. *See, e.g., In re Dill*, 604 F.2d 1356, 1361 (CCPA 1979).

The District Court also concluded "that evidence of other failed attempts supports a finding of non-obviousness."[6] (Ex. 1028 at 26.) The applicant did not address this secondary consideration during patent prosecution. (See Ex. 1002.) Additionally, following the failures that the Patent Owner cited during litigation, but prior to the critical date for the '209 Patent, there were many *successes* in using folic acid supplementation with antifolates to reduce toxicity. The wealth of prior art available by 1999, in fact, shows that folic acid supplementation reduces

[6] The District Court also found "that there was sufficient evidence of skepticism of the claimed invention to support a finding of non-obviousness." (Ex. 1028 at 26.) The applicant did not address this secondary consideration during patent prosecution. (See Ex. 1002.) Additionally, all of the facts upon which the Patent Owner relied for this proposition at trial derive from the Patent Owner's presented trial testimony, rather than from published documents or the '209 Patent's file history. Therefore, prior to discovery regarding the Patent Owner's statements at trial, the Wockhardt does not have access to the evidence necessary to rebut the Patent Owner's claims of skepticism of others.

antifolate toxicity. For example, as described above, *Niyikiza* discloses monitoring homocysteine and MMA levels in patients treated with pemetrexed in a Phase II study, and reported that "[e]levated baseline homocysteine levels (≥ 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA [pemetrexed]." (Ex. 1008 at 127.)

Further, it was also known in the art before 1999 that patients with cancer tend to have elevated levels of plasma homocysteine and that antifolates elevated homocysteine levels. (Ex. 1008 at 126–27; Ex. 1010 at 4, 9.) Therefore, "by 1999, it would have been obvious to a POSA to reduce pretreatment homocysteine levels so that the patient could better tolerate antifolate therapy." (Ex. 1025 ¶ 177.) Thus, a POSA had reason to pretreat the patient with folic acid before starting the patient on antifolate therapy, and the *'974 Patent* discloses that pretreatment with folic acid reduces antifolate toxicity. (*Id.*) Further, pemetrexed clinical trials showed that "[s]upplemental folic acid may play a role in protecting the toxicities associated with antifolate drugs." (*Id.*; Ex. 1016 at 256a.)

In addition, *EP 005* teaches pharmaceutical formulations containing folate and vitamin B12 would reduce antifolate toxicity by reducing antifolate-induced elevated homocysteine levels. (Ex. 1010 at 4.) "In fact, in 1999, both folic acid and vitamin B12 were successfully used to ameliorate methotrexate toxicity in a leukemia patient." (Ex. 1025 ¶ 178; see also Ex. 1020 at 767–68.)

Finally, the District Court's conclusion of non-obviousness based on other failed attempts depends on its finding that "[t]he prior art shows that previous attempts at folic acid supplementation with antifolates reduced toxicity, but at the expense of the drugs' efficacy". (Ex. 1028 at 26.) However, none of the claims of the '209 Patent is directed to the efficacy of the claimed treatment; thus the '209 claims have no nexus to this finding of "unexpected properties," as required for a showing of secondary considerations of non-obviousness. *See Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992.). Moreover, *Carrasco* (Ex. 1020, not before the District Court) is objective evidence of obviousness based on simultaneous invention. *See Trs. of Columbia Univ. v. Illumina, Inc.*, 2015 U.S. App. LEXIS 12343, *30 (Fed. Cir. July 17, 2015) ("[S]imultaneous invention demonstrates what others in the field actually accomplished."); *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) ("simultaneous inventions . . . are persuasive evidence that the claimed apparatus was the product only of ordinary . . . skill.") (internal cites and quotes omitted).

VIII. CONCLUSION

For the foregoing reasons, Wockhardt respectfully requests *inter partes* review of Claims 1–22 of U.S. Patent No. 7,772,209.

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IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,349 words, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,772,209 UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123**, including all exhibits were served on June 30, 2016, via Priority Mail Express® in its entirety on the following:

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