

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.

&

FRESENIUS KABI USA, LLC

PETITIONERS

V.

ELI LILLY & COMPANY

PATENT OWNER

CASE NO.: IPR2016-1343

PATENT NO. 7,772,209

FILED: JULY 11, 2007

ISSUED: AUGUST 10, 2010

INVENTOR: CLET NIYIKIZA

TITLE: ANTIFOLATE COMBINATION THERAPIES

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 7,772,209**

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I. INTRODUCTION

Teva Pharmaceuticals USA, Inc. (“Teva”) and Fresenius Kabi USA, LLC (“Fresenius”) (collectively, “Petitioner”), request an *Inter Partes* Review (“IPR”) of Claims 1–22 (collectively, the “Challenged Claims”) of U.S. Patent No. 7,772,209 (the “’209 Patent”) (Ex. 1001) in accordance with 35 U.S.C. §§ 311–19 and 37 C.F.R. § 42.100 *et seq.*

II. OVERVIEW

The Board has already issued its Decision Instituting *Inter Partes* Review (“Decision”) on all challenged claims of the ’209 patent on the same grounds raised herein. *Neptune Generics, LLC vs. Eli Lilly and Company*, Case IPR2016-00240 (the “Neptune IPR” or “IPR 240”) (Paper 14). In its Decision, the Board found that Petitioner Neptune Generics, LLC (“Neptune”) had demonstrated a reasonable likelihood that claims 1-22 of the ’209 patent are unpatentable for failing to satisfy the nonobviousness requirement of 35 U.S.C. § 103. *Id.* The Board instituted IPR of the challenged claims on the following ground:

Ground 1: Claims 1-22 are obvious in view of Rusthoven in view of EP 005. IPR2016-00240 (Paper 14).

Petitioner Teva/Fresenius hereby files its own petition on the same ground and concurrently seeks joinder of this IPR to the instituted IPR proceedings on these challenged claims.

For the sake of completeness and efficiency, the present Petition is a practical copy of the petition in the Neptune IPR. Specifically, the present Petition is narrowly-tailored to the same claims, prior art, and grounds of unpatentability that are the subject of the Neptune IPR. A motion for Joinder with the Neptune IPR is being filed concurrently with this Petition.

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

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

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

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

For Teva, the real parties-in-interest are Teva Pharmaceuticals USA, Inc., Teva Parenteral Medicines, Inc., Pliva Hrvatska D.O.O., and Barr Laboratories, Inc.¹

¹ The following entities are parent corporations and/or publicly-held companies that own 10 percent or more of the stock of the Teva real parties-in-interest: Sicor Inc.; Teva Pharmaceuticals Holdings Cooperatieve, U.A.; IVAX LLC; Orvet UK; Teva Pharmaceuticals Europe B.V.; Teva Pharmaceuticals Industries Ltd.; Barr Pharmaceuticals, LLC; Ivax International B.V.; IVAX International GmbH; Ivax International (Luxembourg) S.a.r.l.; and IVAX Holdings GmbH.

For Fresenius, the real party-in-interest is Fresenius Kabi USA, LLC.

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

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '209 Patent has been the subject of the following lawsuits: *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); Petition for Inter Partes Review by Sandoz, Inc., IPR2016-00318 (filed June 16, 2016) (“Sandoz IPR”); Petition for Inter Partes Review by Neptune Generics, LLC,

IPR2016-00237 (filed June 3, 2016) (“Neptune IPR 1”);² Petition for Inter Partes Review by Neptune Generics, LLC, IPR2016-00240 (filed June 3, 2016) (“Neptune IPR 2”).

Teva and Fresenius were previously sued by Eli Lilly with respect to the ‘209 patent. *Eli Lilly and Company v. Teva Parental Medicines, Inc., et al.*, INSD-1:10-cv-01376 (filed Oct. 29, 2010) (the “Teva Litigation”). That suit is currently on appeal at the Federal Circuit. *Eli Lilly and Company v. Teva Parenteral Medicines*, No. 15-2067 (Fed. Cir.) (filed Sept. 21, 2015).

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))

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² In addition to the instant petition, Petitioner is also filing petitions and motions for joinder relating to the Sandoz IPR and Neptune IPR 1.

10018-1405, P: (212) 813-8800; F: (212) 355-3333. Petitioner consents to electronic service.

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

The Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 502880 for this Petition for IPR, and further authorizes payment of any additional fees to be charged to this Deposit Account. Any overpayment or refund of fees may also be deposited in this Deposit Account.

VI. 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 binding agent." (*Id.* at 3:1–5.) "A preferred FBP binding agent is folic acid," and a

preferred methylmalonic acid 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 2:14–17.) 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: “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 methylmalonic acid 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) administration of cisplatin in combination with pemetrexed disodium to the patient. (*Id.* at 10:56–12:29.)

The patent also states that a physician determines the amount of methylmalonic acid 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 310³.) 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 methylmalonic acid lowering agent, “those

³ All references to Ex. 1002 pin-cites are to the Bates-labeled page number.

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 311–12.)

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 methylmalonic acid 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 that *Tsao* teaches that “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, Petitioner 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.⁴

⁴ Petitioner 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.)

1. “Patient”

“Patient” means “a human undergoing medical treatment.” (Ex. 1025 at 9, 13; Ex. 1024 ¶ 59; Ex. 1040 ¶ 20.) The Court adopted this same construction with respect to the ’209 Patent in the Teva Litigation.⁵ (Ex. 1025 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. 1024 ¶ 60; Ex. 1040 ¶ 20.) The parties in the Teva Litigation agreed upon a similar construction with respect to the ’209 Patent.⁶ (Ex. 1026 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. 1024 ¶ 61; Ex. 1040 ¶ 20.) The

⁵ In Neptune’s petition, this sentence originally read: “Teva has previously proposed this same construction with respect to the ’209 Patent.” Petitioner has modified this sentence in its petition for accuracy purposes.

⁶ In Neptune’s petition, this sentence originally read: “Teva has previously proposed a similar construction with respect to the ’209 Patent.” Petitioner has modified this sentence in its petition for accuracy purposes.

parties in the Teva Litigation agreed upon this same construction with respect to the '209 Patent.⁷ (Ex. 1026 at 2.)

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. 1024 ¶ 62; Ex. 1040 ¶ 20.) Teva has previously proposed this same construction with respect to the '209 Patent. (Ex. 1026 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. 1024 ¶ 63; Ex. 1040 ¶ 20; Ex. 1001 at 3:59–67.)

⁷ In Neptune’s petition, this sentence originally read: “Teva has previously proposed this same construction with respect to the '209 Patent.” Petitioner has modified this sentence in its petition for accuracy purposes.

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. 1024 ¶ 64; Ex. 1040 ¶ 20; Ex. 1001 at 4:28–44.)

C. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Petitioner 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

Petitioner 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 <i>Rusthoven</i> (Ex. 1011) and <i>EP 005</i> (Ex. 1010).	1011 and 1010

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

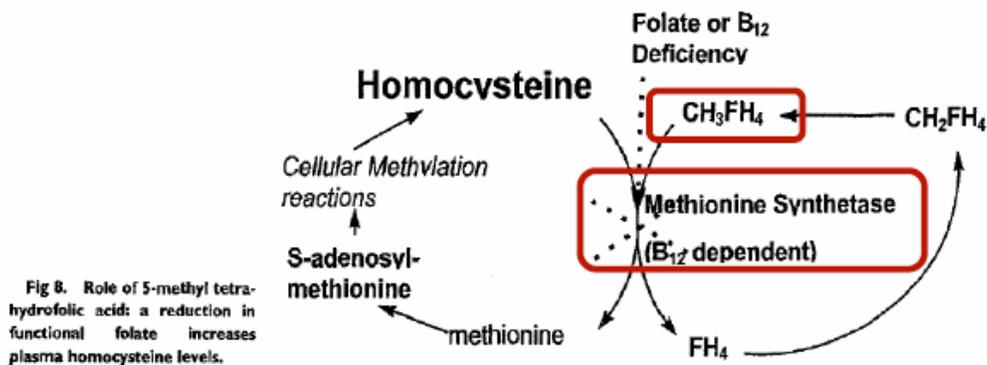
By June of 1999—the earliest possible priority date for the '209 Patent—it was well known in the art that antifolates such as pemetrexed had anticancer properties. (Ex. 1013 at 35; Ex. 1008 at 126; Ex. 1011 at 1194; Ex. 1014 at 3; Ex. 1015 at 99.) Antifolates inhibit folate-dependent enzymes, particularly 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 thymidylate synthase (TS), glycinamide ribonucleotide formyltransferase (GARFT), dihydrofolate reductase (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; Ex. 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:



(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. 1024 ¶ 78; Ex. 1040 ¶ 20.) In fact, as early as 1990, it was well known that elevated methylmalonic acid 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 methylmalonic acid was well known in the prior art as further explained in the figure below:

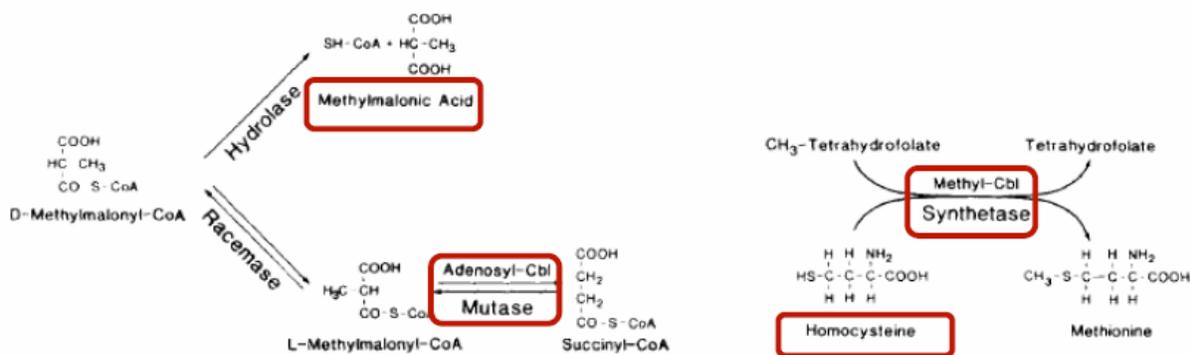


Fig. 2. L-methylmalonyl-CoA mutase (left) and methionine synthetase (right) are the two mammalian Cbl-dependent enzymes. In Cbl deficiency, L-methylmalonyl-CoA accumulates and is converted to D-methylmalonyl-CoA, which is hydrolyzed to methylmalonic acid. Homocysteine accumulates in either Cbl or folate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

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

It was also well known in the art before June 1999 that homocysteine and methylmalonic acid 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 methylmalonic acid 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,

Because 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. 1024 ¶ 86; Ex. 1040 ¶ 20; *see also* Ex. 1020 at 767.) Specifically, in 1999, *Carrasco*⁸

⁸ *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 November 1999 (Ex. 1030 ¶¶ 19–22; 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*

disclosed a study 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 $\mu\text{mol/L}$).” (*Id.* at 768.)

1. Summary of the Petition’s Prior Art References

a. *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 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*

Car, Ltd. v. Canadian Pac. Ry., Ltd., 357 F.3d 1319, 1337-1338 (Fed. Cir. 2004) (same).

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.)

b. *Rusthoven* (Ex. 1011)

Rusthoven constitutes prior art under 35 U.S.C. § 102(b) because it was published and accessible by May 1999 (Ex. 1029 ¶¶ 15–18) in Volume 17, number 4 of the *Journal of Clinical Oncology* in April 1999. (Ex. 1011 at 1194.) The Examiner did not consider *Rusthoven* during prosecution of the '209 Patent. (See Ex. 1001 References Cited.)

Rusthoven discloses a Phase II study of LY231514 (pemetrexed) as first-line chemotherapy for advanced NSCLC. (Ex. 1011 at 1194.) In this study, patients initially received “MTA 600 mg/m² intravenously (‘IV’) for 10 minutes every 3 weeks. After three patients received treatment at this dose, the dose was reduced to 500 mg/m² IV at the same infusion time and frequency because of toxicity seen in this study and another Canadian MTA trial in colorectal cancer.” (*Id.*)

Rusthoven discloses that although MTA was designed as a TS inhibitor, it showed affinity toward other folate-requiring enzymes, including “dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, aminoimidazole carboxamide ribonucleotide formyltransferase, and C1 tetrahydrofolate synthase.” (*Id.*) *Rusthoven* further discloses that “[o]ur group is presently conducting a phase II combination study of MTA and cisplatin in advanced NSCLC.” (*Id.* at 1198.)

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. 1024 ¶ 20; Ex. 1040 ¶ 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.” (Ex. 1024 ¶ 21; Ex. 1040 ¶ 20; *see also* Ex. 1027 at 9.)

VII. 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 *Rusthoven* in view of *EP 005* and the knowledge of one of ordinary skill in the art.

1. Claims 1 and 12 are obvious over *Rusthoven* in view of *EP 005* and the knowledge of one of ordinary skill in the art.

An ordinarily skilled artisan, when seeking to treat patients with pemetrexed—an antifolate known to cause severe side effects—would first look to *Rusthoven* for guidance on “administering pemetrexed disodium” to cancer patients, and would garner from its recommendations for “administering

pemetrexed disodium to a patient in need thereof,” as the **Claim 1** preamble requires. (Ex. 1011 at 1194.) *Rusthoven* is a printed publication in a medical journal on the precise topic of oncology, and therefore, “would be a natural starting point for a POSA to review.” (Ex. 1024 ¶ 104; Ex. 1040 ¶ 20.) *Rusthoven* discloses a Phase II study of LY231514 (pemetrexed) as first-line chemotherapy for advanced NSCLC. (Ex. 1011 at 1194.) From this *Rusthoven* 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 alleged ’209 invention.” (Ex. 1024 ¶ 105; Ex. 1040 ¶ 20.) *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 *Rusthoven* the desirability, when treating patients with pemetrexed disodium, of reducing pemetrexed toxicity by “administering an effective amount of folic acid,” as **Claim 1(a)**⁹ 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

⁹ Claim 1 is divided into elements for ease of explanation.

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. 1024 ¶¶ 106–08; Ex. 1040 ¶ 20.)

Specifically, *Rusthoven* teaches “administering pemetrexed disodium” to a patient, as required by the **Claim 1 preamble and Claim 1(c)**. (Ex. 1011 at 1194; Ex. 1024 ¶ 106; Ex. 1040 ¶ 20.) Further, *Rusthoven* discloses that “folate-requiring enzymes may act as targets for this drug [pemetrexed], including dihydrofolate reductase, glycinamide ribonucleotide formyltransferase” (Ex. 1011 at 1194–95.) It was also well known in the art at the time of the ’209 Patent that antifolate toxicity was associated with elevated blood homocysteine levels. (Ex. 1024 ¶ 107; Ex. 1040 ¶ 20.) Armed with this knowledge and *Rusthoven*’s disclosure, an ordinarily skilled artisan “would have been motivated to look to published methods disclosed in *EP 005* to lower homocysteine levels to reduce pemetrexed toxicity.” (Ex. 1024 ¶ 108; Ex. 1040 ¶ 20; *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.”).

EP 005 teaches that “administering an effective amount of folic acid,” as required by **Claim 1(a)**, to a patient would lower plasma homocysteine levels. (Ex. 1001 at 10:57–58.) From this *EP 005* teaching, 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 **Claim 1(a)** requires. (Ex. 1024 ¶ 109; Ex. 1040 ¶ 20.) 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.* ¶ 110.) 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 have understood from the art available at the time of the invention that methylmalonic acid lowering agent, such as vitamin B12, should be administered to ameliorate pemetrexed toxicity. (*Id.* ¶ 118.) 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 methylmalonic acid lowering agent, such as vitamin B12, should be administered along with folic acid to reduce homocysteine levels. (Ex. 1024 ¶ 111, and ¶¶ 86-87, 164, citing Ex. 1020; Ex. 1040 ¶ 20.) 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 methylmalonic acid lowering agent, such as vitamin B12. (Ex. 1010 at 2; Ex. 1024 ¶¶ 111, 114; Ex. 1040 ¶ 20.) 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. 1024 ¶ 115; Ex. 1040 ¶ 20.)

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. 1024 ¶ 117; Ex. 1040 ¶ 20.) 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 methylmalonic acid 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. 1024 ¶ 118; Ex. 1040 ¶ 20; *see also* Ex. 1010 at 2, 6, 12, 20.) *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, 1027 (Fed. Cir. 2011) (rejecting a claim “as obvious in view of the admitted prior art from the claim preamble and a single cited reference”).

A POSA “seeking to treat cancer patients with chemotherapy drug pemetrexed disodium as in **Claim 12’s preamble**, would look to *Rusthoven* for guidance on ‘administering pemetrexed disodium to a patient in need of chemotherapeutic treatment,’” as the preamble requires. (Ex. 1024 ¶ 119; Ex. 1040 ¶ 20; Ex. 1011 at 1194.) 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 *Rusthoven* the desirability, when treating patients with pemetrexed disodium, of reducing pemetrexed 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. 1024 ¶ 120; Ex. 1040 ¶ 20.) Specifically, *Rusthoven* teaches “administration of pemetrexed disodium,” as **Claim 12(c)** requires. (Ex. 1011 at 1194.)

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 *Rusthoven* the desirability of administering folic acid because *Rusthoven* discloses that “folate-requiring enzymes may act as targets for this drug [pemetrexed], including dihydrofolate reductase, glycinamide ribonucleotide formyltransferase,” and that “dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice.” (Ex. 1011 at 1194–95; *see also* Ex. 1024 ¶ 121; Ex. 1040 ¶ 20.) 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* Ex. 1024 ¶ 122; Ex. 1040 ¶ 20.) For example, *EP 005* discloses that cancers and antifolate methotrexate elevate “blood homocysteine levels,” which cause harmful side effects in patients. (Ex. 1010 at 4, 9; Ex. 1024 ¶ 122; Ex. 1040 ¶ 20.) Thus, a POSA would have been motivated to normalize homocysteine and methylmalonic acid levels in a patient prior to the pemetrexed treatment and would look to

pretreatment methods and dosage ranges disclosed in *EP 005*. (Ex. 1024 ¶ 123; Ex. 1040 ¶ 20.)

Armed with the disclosure of *Rusthoven, EP 005*, and the prior art, an ordinarily skilled artisan would have been motivated to look to the treatment methods and the dosage regimen disclosed in *EP 005* to further implement administration of an effective amount of folic acid and vitamin B12 prior to the pemetrexed treatment. (*Id.*) 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.*, 774 F.3d at 977; see *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.”).

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.” (Ex. 1010 at 6, 20 (emphasis added).) *EP 005* further discloses the dosage regimen and “approximate daily dosages as ($\mu\text{g}/\text{d}/\text{kg}$ 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 the *EP 005*'s folic acid dosage ranges encompass the dosage range recited in **Claim 12(a)**. (Ex. 1024 ¶ 128; Ex. 1040 ¶ 20.) *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.”).

With respect to the folic acid pretreatment limitation of **Claim 12(a)**, although *EP 005* does not explicitly disclose pretreatment with folic acid, because *EP 005* discloses, as described above, “prophylactic treatment for harmful effects associated with elevated homocysteine levels in patients,” it would have been obvious to a POSA that *EP 005* teaches administration of folic acid prior to the administration of antifolate (e.g., pemetrexed disodium). (*See* Ex. 1024 ¶ 124; Ex.

1040 ¶ 20; *see also* Ex. 1010 at 2.) Moreover, it would have been obvious to an ordinarily skilled artisan “treating a patient with folic acid prior to pemetrexed treatment would ameliorate pemetrexed toxicity.” (Ex. 1024 ¶ 129; Ex. 1040 ¶ 20.) *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”).

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. 1024 ¶ 131; Ex. 1040 ¶ 20.) 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. 1024 ¶ 131; Ex. 1040 ¶ 20.) “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. 1024 ¶ 132; Ex. 1040 ¶ 20.)

As described above, a POSA would have understood from the art available at the time of the '209 Patent that cancer and antifolate treatment would cause elevated levels of plasma homocysteine. (Ex. 1024 ¶ 133; Ex. 1040 ¶ 20; *see also* Ex. 1010 at 4, 9; 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. 1024 ¶ 133, and ¶¶ 86-87, 164, citing Ex. 1020; Ex. 1040 ¶ 20.) Also, *EP 005* discloses that “[r]egarding the treatment and prophylaxis of hyperhomocysteinaemia [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. 1024 ¶ 134; Ex. 1040 ¶ 20.)

Moreover, *EP 005* discloses that an unexpected synergism exists when vitamin B12, folic acid... 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. 1024 ¶ 135; Ex. 1040 ¶ 20; *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. 1024 ¶ 135; Ex. 1040 ¶ 20.) Thus, “a POSA seeking to ameliorate pemetrexed toxicity would administer folic acid *along with* vitamin B12 prior to pemetrexed treatment.” (Ex. 1024 ¶ 135 (emphasis added); Ex. 1040 ¶ 20.) *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. 1024 ¶ 137; Ex. 1040 ¶ 20.) *See In re Applied Materials, Inc.*, 692 F.3d 1285, 1295 (Fed. Cir. 2012).

Thus, “a POSA would have been highly motivated to combine *Rusthoven*—which teaches administration of pemetrexed to a patient with advanced NSCLC—with *EP 005*—which teaches administration of pharmaceutical preparations containing folic acid and vitamin B12 in dosage ranges, that encompass claimed dosage ranges, for the prophylactic treatment of elevated levels of homocysteine caused by antifolate treatment,” rendering **Claim 12** obvious. (Ex. 1024 ¶ 138; Ex. 1040 ¶ 20.) *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).)

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 methylmalonic acid 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 methylmalonic acid 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. 1024 ¶ 139; Ex. 1040 ¶ 20.)

In addition to administering vitamin B12 as the methylmalonic acid 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 ($\mu\text{g}/\text{d}/\text{kg}$ 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:

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.)

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. 1024 ¶¶ 140–41; Ex. 1040 ¶ 20.) *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. 1024 ¶ 142; Ex. 1040 ¶ 20.) In fact, the ’209 Patent clearly 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. 1024 ¶ 144; Ex. 1040 ¶ 20.) *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).

With respect to **Claims 6 and 19**—“folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium”—and **Claims 7 and 20**—“folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium”—as previously described, a POSA would understand from *EP 005* that a patient must be treated with folic acid prior to pemetrexed treatment, and that a physician determines the pretreatment regimen based on the patient’s clinical condition. (Ex. 1024 ¶ 145; Ex. 1040 ¶ 20.) As described above with respect to Claim 12(a), *EP 005* discloses a dosage regimen for prophylactic treatment of elevated homocysteine levels. (See Ex. 1010 at 5, 8.) 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.” (Ex. 1010 at 1, 4, 20 (emphasis added).)

Upon reading these disclosures and in view of POSA’s knowledge, as explained above, “it would have been obvious to a POSA to administer folic acid prior to pemetrexed treatment.” (Ex. 1024 ¶¶ 145–46; Ex. 1040 ¶ 20.) And, as explained above, a POSA would adjust the duration of folic acid pretreatment based on patient’s clinical condition, rendering **Claim 6 and 19**—requiring “folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium”—and **Claims 7 and 20**—requiring “folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium”—obvious, because *EP 005* discloses that the dosage regimen is time programmed during different periods of treatment. (Ex. 1024 ¶¶ 145–46; Ex. 1040 ¶ 20.)

Additionally, *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-lingual 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 ($\mu\text{g}/\text{d}/\text{kg}$ 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)	pyridoxal	2 mg
	(ii)	pyridoxine	8 mg; (i) + (ii) = 10 mg
b)		folate	0,65 mg
c)		cyanocobalamin	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 *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 *EP 005* teaches oral administration of folic acid, and the dosage ranges that encompass claimed folic acid dosages. (Ex. 1024 ¶¶ 147–49; Ex. 1040 ¶ 20.) *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.” (*Id.*) See *In re Peterson*, 315 F.3d at 1329–30.

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

Claims 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, *Rusthoven* teaches administering pemetrexed to a patient in need thereof, “while *EP 005* teaches administering folic acid and vitamin B12 in combination with antifolate to a patient.” (Ex. 1024 ¶ 150; Ex. 1040 ¶ 20.) Also, as described above, “*EP 005* also teaches pretreatment with folic acid and vitamin B12,” as first parts of **Claims 13 and 22** require. (Ex. 1024 ¶ 151; Ex. 1040 ¶ 20.)

Additionally, *Rusthoven* discloses administering cisplatin in patients. For example, *Rusthoven* discloses that “[o]ur group is presently conducting a phase II combination study of MTA and cisplatin in advanced NSCLC.” (Ex. 1011 at 1194, 1198 (emphasis added).) Thus, *Rusthoven* teaches “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. 1024 ¶ 152; Ex. 1040 ¶ 20.)

In sum, “in view of administering pemetrexed disodium to phase II cancer patients taught by *Rusthoven*, it would have been obvious to a POSA to implement the administration of an effective amount of folic acid and vitamin B12 disclosed in *EP 005* to reduce pemetrexed toxicity.” (Ex. 1024 ¶ 153; Ex. 1040 ¶ 20.) *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 in accordance with the disclosures in *Rusthoven* would look to published methods for lowering elevated levels of homocysteine levels caused by cancer and pemetrexed treatment—such as 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 two references.” (Ex. 1024 ¶ 154; Ex. 1040 ¶ 20.) *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.”)

At least for these reasons, “it would have been obvious to a POSA to combine *Rusthoven*’s teachings with those of *EP 005* to arrive at the invention claimed in the ’209 Patent.” (Ex. 1024 ¶ 155; Ex. 1040 ¶ 20.) *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 fundamentally different prior art than that used in Petitioner’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.”).

Petitioner contends that Claims 1–22 of the ’209 Patent are obvious under 35 U.S.C. § 103(a) over *Rusthoven* in view of *EP 005* and the knowledge of one of ordinary skill in the art. The District Court did not address either *Rusthoven* or *EP 005*. (See Ex. 1027.) Thus, the District Court’s factual findings related to non-obviousness are not relevant to Petitioner’s challenge. 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. 1024 ¶¶86-87, 178; Ex. 1040 ¶ 20.)

VIII. 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. 1024 ¶ 157; Ex. 1040 ¶ 20.)

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. 1027 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—*Rusthoven* and *EP 005*—described all of the elements of Claims 1–22. (Ex. 1024 ¶ 155; Ex. 1040 ¶ 20.)

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.” (Ex. 1024 ¶ 158; Ex. 1040 ¶ 20.)

Further, applicant provides no independent data to support their 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. 1024 ¶ 159; Ex. 1040 ¶ 20.) 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.”¹⁰ (Ex. 1027 at 26.) The applicant did not

¹⁰ The District Court also found “that there was sufficient evidence of skepticism of the claimed invention to support a finding of non-obviousness.” (Ex. 1027 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

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 antifolate toxicity. For example, as described above, *Rusthoven* discloses a Phase II study of pemetrexed as first-line chemotherapy for advanced NSCLC. (Ex. 1011 at 1194.) It also discloses that “folate-requiring enzymes may act as targets for this drug [pemetrexed], including dihydrofolate reductase, glycinamide ribonucleotide formyltransferase,” and that “dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice.” (*Id.* at 1194–95.)

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; Ex. 1010 at 4, 9; Ex. 1012 at 411, 412.) 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. 1024 ¶ 163; Ex. 1040 ¶ 20.) Thus, a POSA had reason to pretreat the patient

history. Therefore, prior to discovery regarding the Patent Owner’s statements at trial, the Petitioner does not have access to the evidence necessary to rebut the Patent Owner’s claims of skepticism of others.

with folic acid before starting the patient on antifolate therapy, and *EP 005* discloses that pretreatment with folic acid reduces antifolate toxicity. (*Id.*) Further, clinical trials with pemetrexed 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 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. 1024 ¶ 164; Ex. 1040 ¶ 20; *see also* Ex. 1020 at 767–68.)

Finally, the District Court’s conclusion of non-obviousness based on other failed attempts, like its conclusion regarding unexpected properties, 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. 1027 at 26.) However, as previously discussed, 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.). 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) (“Independently made, simultaneous inventions, made ‘within a comparatively short space of time,’ are persuasive evidence that the claimed apparatus ‘was the product only of ordinary mechanical or engineering skill.”) (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925)); *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) (“The fact of near-simultaneous invention ... is strong evidence of what constitutes the level of ordinary skill in the art.”)).

IX. CONCLUSION

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

Respectfully Submitted,

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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 11,701 words, excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: July 1, 2016

/Gary J. Speier/
Gary J. Speier, Lead Counsel

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), this is to certify that on July 1, 2016, I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,772,209, including all exhibits (Exhibits 1001-1041) by EXPRESS MAIL on Patent Owner, counsel of record for Eli Lilly and Company and counsel of record for Petitioner in IPR2016-00240 for U.S. Patent No. 7,772,209 at its correspondence address as follows:

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