Paper No. ___
July 8, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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 PURSUANT TO 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42

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I. INTRODUCTION

On June 16, 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 IPR2016-00318. In its decision of institution, the Board determined that it is reasonably likely that claims 1-22 of the '209 Patent would have been obvious in view of the following:[1]

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

Sandoz, Inc. v. Eli Lilly & Company, No. IPR2016-00318, Paper 14 at 21 (PTAB June 16, 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. §103(a) over (1) Calvert in view of Niyikiza I, Worzalla, and the

[1] The Board slightly modified the Grounds of unpatentability set forth in the Sandoz IPR by substituting EP '005 and the '974 Patent for the knowledge of a person of ordinary skill.

knowledge of a person of ordinary skill; and (2) Calvert in view of Niyikiza I, Hammond I and the knowledge of a person of ordinary skill. This petition presents the same arguments, based on the same prior art presented in the IPR2016-00318 Petition (IPR2016-00318, Paper 1), and on which the Board instituted IPR in IPR2016-00318, along with a Motion for Joinder to join this Petition with the IPR2016-00318 proceedings. Indeed, this petition is an almost verbatim copy of the petition in IPR2016-00318.[2]

For the reasons explained below, and for the reasons the Board instituted IPR in IPR2016-00318, Wockhardt is reasonably likely to prevail on Grounds 1 and 2 with respect to the challenged claims. Wockhardt requests that this Board institute this IPR and cancel each of claims 1-22 of the '209 Patent.

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. *Sandoz Inc. v. Eli Lilly and Company*, Case IPR2016-00318 (the "Sandoz IPR" or "IPR 318") (Paper 14). In its Decision, the Board found that

[2] Wockhardt's intention is to copy the relevant portions of IPR2016-00318 verbatim. To the extent discrepancies exist between the respective petitions, those differences are due to solely to transcription errors.

Petitioner Sandoz Inc. ("Sandoz") 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 grounds:

> Ground 1: Claims 1-22 are obvious over Calvert in view of Niyikiza I, Worzalla, and the knowledge of a person of ordinary skill.
>
> Ground 2: Claims 1-22 are obvious over Calvert in view of Niyikiza I, Hammond I, and the knowledge of a person of ordinary skill.

IPR2016-00318 (Paper 14). Petitioner Wockhardt 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 Sandoz IPR. Specifically, the present Petition is narrowly-tailored to the same claims, prior art, and grounds of unpatentability that are the subject of the Sandoz IPR, and, in addition, relies on the same expert as the Sandoz IPR. A motion for Joinder with the Sandoz IPR is being filed concurrently with this Petition.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest

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").

B. Related Matters

1. Related Litigations

Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '209 Patent. The Patent Owner has asserted the '209 Patent in the following litigations: 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).

On March 31, 2014, the U.S. District Court for the Southern District of Indiana ruled in the Teva Litigation that Teva failed to establish by clear and convincing evidence that claims 9, 10, 12, 14, 15, 18, 19, and 21 of the ’209 patent are invalid as obvious under 35 U.S.C. § 103. Ex. 1003, Teva Decision at 9-27. An appeal of the Teva Decision is currently pending in the Federal Circuit. *Eli Lilly & Co. v. Teva Parenteral Meds.*, No. 1:10-cv-1376, 2015 U.S. Dist. LEXIS 112221 (S.D. Ind. Aug. 25, 2015), *appeal docketed*, No. 15-2067 (Fed. Cir. Sept. 25, 2015).

The Teva Decision is not binding in this proceeding. *See Noven Pharm., Inc. v. Novartis AG*, No. IPR2014-549, 2015 WL 5782080, at *2 (PTAB Sept. 28, 2015) ("[W]hile we have considered the Federal Circuit's decision, we have independently analyzed patentability of the challenged claims based on the evidence and standards that are applicable to this proceeding."); *In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1297 (Fed. Cir. 2007) (finding the PTO, in a reexamination procedure, was not bound by prior district court litigation to which it was not a party). Moreover, the district court made erroneous factual and legal findings that if corrected would likely have led to a different outcome under the standards applicable in that proceeding.

2. Related Proceedings Before the Board

The '209 Patent has also been challenged before the Board in the following proceedings in which Petitioner was not and is not a party: *Accord Healthcare, Inc., USA v. Eli Lilly & Co.*, IPR2013-356 (PTAB, filed June 14, 2013); *Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-237 (PTAB, filed November 24, 2015) ("Neptune IPR 1"); *Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-240 (PTAB, filed November 24, 2015) ("Neptune IPR 2"); *Sandoz Inc. v. Eli Lilly & Co.*, IPR2016-318 (PTAB, filed December 14, 2015); *Apotex Inc. & Apotex Corp. v. Eli Lilly & Company,* IPR2016-01190 (PTAB, filed July 1, 2016); *Apotex Inc. and Apotex Corp. v. Eli Lilly & Company*, IPR2016-01191 (PTAB, filed July 1,

2016); *Teva Pharmaceuticals USA, Inc. and Fresenius Kabi USA, LLC v. Eli Lilly & Company*, IPR2016-01340 (PTAB, filed July 1, 2016); *Teva Pharmaceuticals USA, Inc. and Fresenius Kabi USA, LLC v. Eli Lilly & Company*, IPR2016-01341 (PTAB, filed July 1, 2016); *Teva Pharmaceuticals USA, Inc. and Fresenius Kabi USA, LLC v. Eli Lilly & Company*, IPR2016-01343 (PTAB, filed July 1, 2016); *Wockhardt Bio AG v. Eli Lilly & Company,* IPR2016-01335 (PTAB, filed July 1, 2016) and *Wockhardt Bio AG v. Eli Lilly & Company,* IPR2016-01337 (PTAB, filed July 1, 2016).

C. Lead and Back-Up Counsel

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. GROUNDS FOR STANDING

As required by 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 on the grounds identified herein.

VI. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioner requests *inter partes* review and cancellation of claims 1-22 of the '209 Patent on one or more of grounds pursuant to 35 U.S.C. § 103 as set forth herein. The '209 Patent is to be reviewed under pre-AIA § 103. Petitioner's detailed statement of the reasons for the relief requested is set forth below in the section titled "Statement of Reasons for the Relief Requested." In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. In addition, the Petition is accompanied by the declaration of Dr. Ron D. Schiff, Ex. 1004.

Claims 1-22 of the ’209 Patent are unpatentable based upon the following grounds:

Ground 1: Claims 1-22 are obvious over Calvert in view of Niyikiza I, Worzalla, and the knowledge of a person of ordinary skill.

Ground 2: Claims 1-22 are obvious over Calvert in view of Niyikiza I, Hammond I, and the knowledge of a person of ordinary skill.

The addition of limitations directed to specific dosages, dosing schedules, and the combination of the known chemotherapy drug cisplatin add nothing patentable to independent claims 1 and 12 because these parameters were well known to the person of ordinary skill in the art (“POSA”).

There is no redundancy in Grounds 1 and 2. Ground 1 (which is directed to claims 1-22) relies on Calvert, Niyikiza I, and Worzalla as primary references. Worzalla expressly discloses folic acid pretreatment in mice. Ground 2 (which is also directed to claims 1-22) differs because it relies on Hammond I as the third primary reference. Hammond I expressly discloses folic acid pretreatment in humans.

VII. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

This petition meets the threshold requirement for *inter partes* review because it establishes “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. §

314(a). As explained below, for each of the grounds of unpatentability proposed below, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VIII. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

Pemetrexed is the active pharmaceutical ingredient in Lilly's Alimta® chemotherapy product, which was approved by the U.S. Food & Drug Administration ("FDA") in February 2004. Ex. 1038, Alimta® Approval Letter. In the early 1990s, Lilly obtained patent coverage for pemetrexed with the issuance of U.S. Patent Nos. 5,217,974 ("'974 Patent") and 5,344,932 ("'932 Patent"). The '974 Patent expired in 2012 and patent exclusivity for the '932 Patent will expire in 2017. Ex. 1025, Orange Book Listing for Alimta® at 1025-0003; Ex. 1053, 2015 Alimta® Orange Book Listing. The '209 Patent, which expires in 2022, is Lilly's effort to extend its patent monopoly for pemetrexed for an additional 5 years beyond the 2017-expiration date of Lilly's '932 Patent. But the claims of the '209 Patent are directed to an obvious method for administering the known drug pemetrexed disodium. As such, the claims of the '209 Patent should be canceled, and Lilly's patent monopoly over pemetrexed should end with the expiration of the '932 Patent in 2017, which will clear the way for Petitioner's lower-priced generic product.

In the late 1990s, pemetrexed was one of several known antifolates, which are a class of antitumor drugs. Antifolates interfere with the growth and proliferation of cancer cells by disrupting DNA synthesis. Ex. 1004, Schiff Decl. ¶ 28. Antifolates disrupt DNA synthesis by competing with folic acid (actually the metabolic derivatives of folic acid) for binding sites on certain enzymes. *Id.* ¶ 30. Unfortunately, antifolates also interfere with the growth and proliferation of healthy cells, which leads to "toxicity." *Id.* ¶ 29. In order to maintain sufficient folate pools to support DNA synthesis in healthy cells (but not faster reproducing cancer cells), it was known to pretreat patients with appropriate amounts of folic acid prior to starting therapy with antifolates such as pemetrexed. *Id.* ¶ 39; Ex. 1005, '974 Patent, 2:1-24, 6:22-47; Ex. 1015, Hammond I; Ex. 1014, Hammond II; Ex. 1012, Mendelsohn at 270.

Lilly's '209 Patent is generally directed to adding vitamin B_{12} to this known folic acid pretreatment regimen. However, more than a year before the earliest claimed priority date (June 2000), it would have been obvious to add vitamin B_{12} to a folic acid pretreatment regimen prior to starting pemetrexed therapy. Here's why:

First: It was known that pemetrexed's toxicity is highly correlated with elevated baseline homocysteine levels. Ex. 1007, Calvert at 8-9; Ex. 1006, Niyikiza I at 126-27.

Second: It was known that both folic acid and vitamin B_{12} are required for cells to convert homocysteine into methionine and thus a POSA would understand that both folic acid and vitamin B_{12} should be administered to reduce the elevated baseline homocysteine levels associated with pemetrexed toxicity. Ex. 1007, Calvert at 8-9.

Third: It was known that folic acid pretreatment reduces the severity or prevalence of pemetrexed toxicity. Ex. 1007, Calvert at 8-9; Ex. 1013, Worzalla at 3235; Ex. 1014, Hammond II at 866; Ex. 1015, Hammond I at 620P.

Therefore, in view of the known correlation between pemetrexed's toxicity and a deficiency of either folic acid or vitamin B_{12}, as explained by Calvert (citing Niyikiza's work), a POSA would have been highly motivated to add vitamin B_{12} to the known folic acid pretreatment regimen of Worzalla and Hammond I. The reasonably expected result: normalization of baseline homocysteine levels with a corresponding reduction in the severity and/or prevalence of pemetrexed toxicity. Ex. 1004, Schiff Decl. ¶¶ 66-90.

Accordingly, Calvert and Niyikiza I in view of Worzalla or Hammond I teach precisely what is recited in claims 1-2 of the '209 Patent, namely, pretreating a patient with folic acid and a MMA lowering agent (e.g., vitamin B_{12}) prior to administering pemetrexed. Claims 3-22 of the '209 Patent add nothing patentable to claims 1-2, but instead recite art-recognized dosing schedules for the known

vitamins, folic acid and vitamin B_{12}, and/or require administering pemetrexed with another known chemotherapy drug, cisplatin, a combination therapy that was also known in the prior art. Ex. 1017, Thödtmann, Abstract. Accordingly, all of the claims of the '209 Patent are obvious over Calvert and Niyikiza I in combination with Worzalla or Hammond I alone or in further view of the additional prior art discussed herein.

B. Background of the '209 Patent

1. Prior Art Administration of Pemetrexed Resulted in Toxicity Caused by Elevated Homocysteine Levels

By June 1999, which is one year before 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. 1047, Calvert & Walling at 35; Ex. 1001, '209 patent, 1:19-49; Ex. 1004, Schiff Decl. ¶ 27.

As previously noted, antifolates inhibit folate-dependent enzymes, particularly enzymes involved in the synthesis of precursors of deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA"). Ex. 1047, Calvert & Walling at 35; Ex. 1004, Schiff Decl. ¶¶ 30. 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. Ex. 1047, Calvert & Walling at 35; Ex. 1004, Schiff Decl. ¶ 28.

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 can be severe and even life-threatening. Ex. 1047, Calvert & Walling at 35; Ex. 1001, '209 patent, 1:11-14; Ex. 1004, Schiff Decl. ¶ 52.

The '209 Patent concerns methods of treating patients with a previously discovered antifolate, pemetrexed disodium.[3] Pemetrexed is also known as LY231514 or multitargeted antifolate ("MTA"), a name derived from the fact that pemetrexed is a folate analog that inhibits not one, but several enzymes in the folate pathway, including thymidylate synthase ("TS"), glycinamide ribonucleotide formyltransferase ("GARFT"), dihydrofolate reductase ("DHFR"), and aminoimidazole carboxamide ribonucleotide formyltransferase ("AICARFT"). Ex. 1047, Calvert & Walling at 35; Ex. 1004, Schiff Decl. ¶ 35.

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. Ex. 1047, Calvert & Walling at 38.

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[3] Lilly's prior art '932 Patent discloses that the "mono and disodium salts [of pemetrexed], particularly the disodium salt, are advantageous." Ex. 1034, '932 patent, 2:47-48.

From these studies and others, it was known that toxicity limits the administration of pemetrexed. *Id.*; Ex. 1006, Niyikiza I at 126; Ex. 1001, '209 Patent, 1:62–64.

By June 1999, published research indicated a link between elevated baseline levels of blood homocysteine and patients who experienced pemetrexed toxicities. Ex. 1001, '209 Patent at 2:14–26; Ex. 1007, Calvert at 8–9; Ex. 1006, Niyikiza I; Ex. 1016, Niyikiza II. The prior art also indicated that high homocysteine results from deficiencies in folic acid and/or vitamin B_{12}. *E.g.*, Ex. 1007, Calvert at 8-9.

2. It Was Well-Known that Elevated Baseline Homocysteine Levels Are Most Effectively Treated by Administering Both Folic Acid and Vitamin B_{12}

As of June 1999, the POSA would have understood that a patient presenting with elevated homocysteine levels should receive both folic acid and vitamin B_{12} supplementation. This is evidenced by the teachings of multiple references published prior to June 1999. *See* Ex. 1004, Schiff Decl. ¶ 75.

For example, Brattström is an article titled "Vitamins as Homocysteine-Lowering Agents," published in 1996 in Journal of Nutrition, Vol. 126, pp. 1276S-1280S. Ex. 1020, "Brattström." Brattström is prior art under 35 U.S.C. § 102(b) and is not listed on the face of the '209 Patent as having been of record during prosecution. Brattström teaches methods for lowering elevated homocysteine levels in patients with moderate hyperhomocysteinemia. Specifically, Brattström recites that "folate and vitamin B-12 deficiency may result

in considerable hyperhomocysteinemia, which is rapidly normalized after replenishment with the deficient vitamin." *Id.* at 1276S. Brattström further teaches that the combination of folate and vitamin B_{12} is required even in subjects with "low normal" vitamin B_{12} concentrations because a "full response to folic acid cannot be achieved unless vitamin B-12 is given concomitantly." *Id.* at 1277S; Ex. 1004, Schiff Decl. ¶ 76.

Brattstrom's teaching is further buttressed by other prior art publications under 35 U.S.C. § 102(b), which similarly instructed that:

- It is "essential that vitamin B-12 and folate be combined to treat hyperhomocysteinemia" (Ex. 1039, Ubbink I, at 1931);
- "[V]itamin B-12 may be beneficial when included in supplements or in a food-fortification regimen together with folic acid." (Ex. 1040, Brönstrup, Abstract & 1109); and
- "Although folic acid is the most powerful [total homocysteine] tHcy-lowering agent, this does not imply that vitamin B_{12} and vitamin B_6 may be omitted in the treatment of moderate hyperhomocyst(e)inemia. Vitamin B_{12} supplementation has a small, but significant effect in circulating tHcy concentrations…" (Ex. 1041, Ubbink II at 321).

Thus, POSA would have been motivated to rectify a deficiency in folic acid and/or vitamin B_{12} to lower elevated homocysteine levels associated with pemetrexed

toxicity by administering both folic acid and vitamin B_{12} prior to initiating pemetrexed therapy. Ex. 1004, Schiff Decl. ¶¶ 74-79.

3. The '209 Patent

The '209 Patent contains 22 claims of which claims 1 and 12 are independent. Both claims 1 and 12 are directed to methods for: (i) treating a patient with the antifolate pemetrexed disodium in which the patient receives pretreatment with both (ii) folic acid and (iii) a methylmalonic acid lowering agent, which claim 12 specifically requires to be vitamin B_{12}. The dependent claims add limitations requiring: (1) standard dosages for folic acid and vitamin B_{12}; (2) standard dosing schedules for folic acid and vitamin B_{12}; and (3) the additional administration of the known chemotherapy drug cisplatin.

4. The Prosecution of the '209 Patent

During prosecution, Applicant faced obviousness rejections based on a combination of four sets of references teaching: (i) pemetrexed disodium ('932 patent); (ii) the antitumor effects of vitamin B_{12}; (iii) folic acid pretreatment for pemetrexed (Worzalla); and (iv) cisplatin. Ex. 1002, '209 file history at 121-29 (Feb. 8, 2009 Office Action); *Id*. at 364-70 (Sept. 8, 2009 Office Action).

In an effort to overcome these rejections, Applicant argued, inter alia, that the POSA would not pretreat with folic acid or vitamin B_{12} because "it was

standard of care to avoid vitamins in patients undergoing chemotherapy . . . ." *Id.* at 448 (Nov. 13, 2009 Remarks at 8). In support of this contention, the Applicant relied on several references addressing antifolates other than pemetrexed, namely, raltitrexed, methotrexate, and fluorouracil (5-FU). *Id.* at 448-49. Contrary to the Applicant's arguments, however, the references state that "[f]olate deficiency states may increase methotrexate toxicity" and that 5FU is "contraindicated for patients in a poor nutritional state," and thus suggest pretreatment with folic acid. Ex. 1002, '209 file history at 449 (November 13, 2009 Amendment at 9), 470 (PDR, Methotrexate); *Id.* at 611 (PDR, 5-FU). Moreover, all of the references relied on by Applicant are silent as to whether vitamin B_{12} should be administered with antifolates. *Id.* at 466-72, 480-82, 608-11.

Applicant also argued that Worzalla, which is specific to pemetrexed, "discloses that the addition of folic acid may reduce the effectiveness of pemetrexed disodium." *Id.* at 451 (Nov. 13, 2009 Remarks at 11). But Applicant's characterization is contrary to the express disclosure of Worzalla, which actually reached the exact opposite conclusion: "Folic acid supplementation was demonstrated to preserve the antitumor activity of LY231514 *[i.e.*, pemetrexed] while reducing toxicity." Ex. 1013, Worzalla, Abstract (emphasis added); Ex. 1037, Bajetta at 1543, 1547. The Examiner failed to confront Applicant about its incorrect characterization of Worzalla and subsequently allowed the claims without

comment. Ex. 1002, '209 file history at 861-74 (Mar. 10, 2010 Notice of Allowability).

The Examiner also did not squarely address Niyikiza's teaching that pemetrexed toxicity could be predicted by elevated pre-treatment levels of homocysteine. The Examiner did not have the benefit of Hilary Calvert's An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents, Seminars Oncology, 26: 3-10 (1999) (Ex. 1007), which explained that the elevated homocysteine levels associated with pemetrexed toxicity are caused by a folic acid and/or vitamin B_{12} deficiency. Ex. 1007, Calvert at 8-9. Thus, the Examiner apparently did not appreciate the art-recognized connection between a deficiency of either folic acid or vitamin B_{12} and pemetrexed toxicity – a connection that would have motivated a POSA to add vitamin B_{12} to the folic acid pretreatment regimens of Worzalla and Hammond I.

C. Person of Ordinary Skill in the Art

The subject matter of the '209 Patent draws from several disciplines, and as such, the patent is directed to a collaborative team of individuals in which each person would have been able to draw upon the experiences and knowledge of the others. In particular, the person of ordinary skill in the art ("POSA") at the time of the alleged invention would have been a medical doctor experienced in oncology with knowledge and/or several years of experience regarding the use of antifolates

in the treatment of cancer and additional qualifications or experience in the field of nutritional sciences involving vitamin deficiencies. Ex. 1004, Schiff Decl. ¶ 13.

D. Claim Construction

The claim terms in the '209 Patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation ("BRI") of the claim language. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278-79 (Fed. Cir. 2015). Petitioner does not believe that any special meanings apply to the claim terms in the '209 Patent. Petitioner's position regarding the scope of the claims should not be taken as an assertion regarding the appropriate claim scope in other adjudicative forums where a different claim interpretation standard may apply.

1. "Patient"

Under the BRI, the term "patient," which appears in the preambles of claim 1 (a "patient in need thereof") and claim 12 ("a patient in need of chemotherapeutic treatment"), means "mammal," *i.e.*, all mammals, and is not limited to just humans. This construction is mandated by the BRI in view of the intrinsic record.[4]

[4] Neptune Generics, LLC's recently-filed IPR petitions for the '209 Patent incorrectly state that Teva proposed that "'[p]atient' means 'a human undergoing

The term "patient" is not explicitly defined in the '209 Patent specification. The specification does, however, use the term "patient" to encompass mammals generally and does not specifically limit the term to humans. For example, the '209 specification uses the terms "mammal" and "patient" interchangeably. *See* Ex. 1001, '209 Patent, 4:4-27 (using the terms interchangeably when defining the phrase "in combination with"); *id*. at 6:35-54 (using the terms interchangeably in describing an especially preferred embodiment). Moreover, the claimed dosage ranges and schedules recited for a "patient" in claims 6-8, 19, and 20 are the same ranges and schedules recited in the specification as the preferred embodiment for a "mammal." Compare *id*. at 6:22-40, with *id*., claims 6-8, 19, and 20.

The prosecution history further indicates that the BRI of "patient" is "mammal." During prosecution of U.S. Pat. App. No. 11/288,807, a parent application of the '209 Patent, the Applicant presented a draft claim to a "method of inhibiting tumor growth in humans . . . ." Ex. 1024, '807 file history at 38, (November 29, 2005 Preliminary Amendment at 3). Later, during prosecution of the application that issued as the '209 Patent, the claims were preliminarily

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medical treatment.'" *E.g.*, IPR2015-237, Paper No. 1, at 13. The record in the Teva Litigation indicates that Teva opposed this construction as contrary to the intrinsic record. Ex. 1035, Joint Claim Construction Statement at 2.

amended to recite an "improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment . . . ." Ex. 1002, '209 file history at 3, (July 11, 2007 Preliminary Amendment at 3). The patentee knew how to limit the scope of the claims to treatment of a "human" when that was the intention. *See*, *e.g.*, *Novo Nordisk A/S v. Eli Lilly & Co.*, No. 98-643, 1999 WL 1094213, at *17 (D. Del. Nov. 18, 1999) ("[I]f Lilly had desired to limit the claims to 'human patients,' it could have used that language instead of 'patient.' Since Lilly chose to use the broader term[ ] . . . 'patient,' the scope of the claims should reflect its choice of words.").

The extrinsic evidence also supports Petitioner's BRI of "patient." Technical literature confirms that the term "patient" is not necessarily limited to humans, but may encompass mammals generally. *See* Ex. 1008, Animal Medicine at 1005-1028 (referring repeatedly to animals as "patients" in the context of administering oncology drugs). Courts have relied on extrinsic evidence to construe the term "patient" in similar claims to include all animals. *See*, *e.g.*, *Novo Nordisk*, 1999 WL 1094213, at *16-17 (construing "patient" to include all animals).

Further, the district court's adoption in the Teva Litigation of a narrow interpretation of "patient" as restricted to humans is not binding on the Board and provides no basis to deviate from the BRI construction of "patient" as "mammal."

See In re Am. Acad. of Sci. Tech Ctr., 367 F.3d 1359, 1369 (Fed. Cir. 2004) (finding the Board's construction of the term "user computer" was proper, even though it differed from the district court's claim construction, as "the PTO is obligated to give claims their broadest reasonable interpretation during examination").

Regardless of whether the term "patient" is properly construed to mean mammals or narrowly interpreted as limited solely to humans, all of the claims of the '209 Patent are obvious for the reasons set forth below.

2. The "Effective Amount" Limitations

Lilly previously agreed to the constructions set forth below for the "effective amount" limitations and is therefore estopped from advocating different positions in this proceeding. Ex. 1035, Joint Claim Construction Statement at 1-2. *See Key Pharm. Inc. v. Hercon Labs. Corp.*, 161 F.3d 709, 714-15 (Fed. Cir. 1998) (noting arguments that a trial court erred in adopting the party's own claim construction are treated "with extreme disfavor" and may result in estoppel). In addition, these constructions are consistent with the BRI of these limitations in view of the intrinsic record and therefore should be adopted by the Board. *See* Ex. 1001, '209 Patent at 3:53-58 ("As used herein, the term 'effective amount' refers to an amount of a compound or drug, which is capable of performing the intended result . . . ."). Those constructions are reproduced below:

- "**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."
- "**an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent**" means "amounts of folic acid and a methylmalonic aid lowering agent that are capable of reducing the prevalence or severity of one or more toxicities associated with the administration of pemetrexed disodium."

Ex. 1035, Joint Claim Construction Statement at 1-2.

3. "Methylmalonic Acid Lowering Agent"

Lilly previously agreed to the following construction of "methylmalonic acid lowering agent" and is estopped from now disavowing that construction: "an agent such as vitamin B_{12} which can be used to lower the concentration of methylmalonic acid in a mammal." Ex. 1035, Joint Claim Construction Statement at 2; see Key, 161 F.3d at 714-15. This construction is consistent with the BRI and should be adopted by the Board.

E. Patents and Printed Publications Relied on in this Petition

1. Calvert (Ex. 1007) Teaches that Elevated Baseline Homocysteine Levels Associated with Pemetrexed Toxicity Are Caused by Either Folic Acid or Vitamin B_{12} Deficiencies

Calvert is an article titled "An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents," published in April 1999 in Seminars in Oncology, Vol. 26, No 2, Suppl. 6, pp. 3-10. Ex. 1007, Calvert. Calvert is prior art under 35 U.S.C. § 102(b). Calvert is not listed on the face of the patent as having been of record during the prosecution of the application that issued as the '209 Patent. Nor did the District Court in the Teva Litigation analyze Calvert in its opinion. Ex. 1003, Teva Decision.

Calvert discusses the impact of antifolates generally on intracellular folate metabolism, and focuses on pemetrexed specifically, which Calvert characterizes as having an "encouraging level of activity documented in early phase II clinical trials." Ex. 1007, Calvert at 9 (citing Ex. 1047, Calvert & Walling). Calvert also links both vitamin B_{12} and folic acid deficiencies with elevated homocysteine levels as a predictor of pemetrexed toxicity:

> any functional deficiency either in B_{12} or folate will result in . . . [an] increase in the plasma level of homocysteine. The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA.

Ex. 1007, Calvert at 8-9 (citing Ex. 1016, Niyikiza II) (endnotes omitted). Thus, POSA would have understood from Calvert that pemetrexed was a promising new antifolate. Further, POSA would have understood the importance of rectifying a folic acid and/or vitamin B_{12} deficiency prior to initiating pemetrexed therapy. Ex. 1004, Schiff Decl. ¶ 87.

2. Niyikiza I (Ex. 1006) Teaches a Strong Correlation between Baseline Homocysteine Levels and Pemetrexed Toxicity

Niyikiza I is an abstract titled "MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity," published in 1998 in Annals of Oncology, Abstract 609P, Supplement 4 to Volume 9. Ex. 1006. Niyikiza I is prior art under 35 U.S.C. § 102(b).

Niyikiza I is a statistical analysis that demonstrated the correlation between increased homocysteine (Hcys) levels and pemetrexed toxicity. Specifically, Niyikiza I described a study of 139 patients treated with pemetrexed during a phase II trial. Ex. 1006, Niyikiza I. The patients were monitored for changes in vitamin metabolite levels, including homocysteine.

An analysis was then conducted to identify correlations between vitamin levels of patients receiving pemetrexed therapy and toxicity. Niyikiza I concluded that:

> [t]oxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥ 10 μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA.

Id. Thus, Niyikiza I taught that patients with levels above 10μM of homocysteine (indicating only subclinical vitamin deficiency) were predisposed to pemetrexed toxicity. Ex. 1004, Schiff Decl. ¶¶ 68-69.

3. Worzalla (Ex. 1013) Teaches Pretreating Animal Patients with Folic Acid before Pemetrexed Therapy

Worzalla is an article titled "Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514," published in 1998 in Anticancer Research 18:3235-40. Ex. 1013. Worzalla is prior art under 35 U.S.C. § 102(b).

Worzalla reports the results of preclinical studies on mice involving folic acid pretreatment with pemetrexed, which were performed at Lilly's facilities. Worzalla concludes that "folic acid can be manipulated to achieve greater therapeutic effects," and "[f]olic acid supplementation was demonstrated to preserve the antitumor activity of [pemetrexed] while reducing toxicity." *Id.* at 3235, 3238. Worzalla thus teaches that folic acid pretreatment should be administered in an amount sufficient to satisfy healthy cells (*i.e.*, reduce

pemetrexed's toxicity) but below those levels sufficient to satisfy the relatively higher folate needs of cancer cells *(i.e.*, without completely neutralizing pemetrexed's therapeutic effect). Ex. 1004, Schiff Decl. ¶¶ 57-62.

4. Hammond I (Ex. 1015) Teaches Pretreating Human Patients with Folic Acid before Starting Pemetrexed Therapy

Hammond I is an abstract titled "A phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)," published in 1998 in Annals of Oncology, Abstract 620P, Supplement 4 to Volume 9. Ex. 1015 at 620P. Hammond I is prior art under 35 U.S.C. § 102(b).

Hammond I reported the results of a phase I clinical trial in which human patients received 5 mg/day of folic acid starting two days before treatment with pemetrexed at doses ranging from 600-925 mg/m2. Hammond I states that "preclinical evaluations indicate that FA [*i.e.*, folic acid] supplementation increases the therapeutic index of MTA [*i.e.*, pemetrexed disodium]," and concluded that folic acid "supplementation appears to permit MTA dose escalation by ameliorating toxicity." *See* Ex. 1015, at 620P; *see also* Ex. 1036, Teva Litigation Trial Tr. 1216:6-1218:12. Hammond's prior abstract ("Hammond II") reported a partial response in a patient with metastatic colon cancer (Ex. 1014), further confirming that the folic acid pretreatment regimen with pemetrexed provided a

therapeutic benefit. Ex. 1004, Schiff Decl. ¶¶ 54-56; Ex. 1014, Hammond II at 866.

The Hammond abstracts list Lilly's facilities as the source of the reported studies.

F. The Challenged Claims Are Unpatentable as Obvious over the Prior Art

As discussed herein, each limitation of the claims of the '209 Patent is disclosed in the prior art, and a POSA would have been motivated to combine the prior art teachings to arrive at the claimed invention.

1. Calvert and Niyikiza I Would Have Motivated a POSA to Add Vitamin B_{12} to the Folic Acid Pretreatment Regimen of Worzalla or Hammond I

a. A POSA Would Know to Pretreat patients with Vitamin B_{12} to Reduce High Homocysteine Levels Linked to Pemetrexed Toxicity

The only difference between claims 1-2 of the '209 Patent and the prior art disclosures of Worzalla and Hammond I is that the patients in Worzalla and Hammond I did not receive a methylmalonic acid ("MMA") lowering agent such as vitamin B_{12}. However, a POSA would have recognized that administering vitamin B_{12} was the logical next step for reducing pemetrexed toxicity based upon the teachings of Calvert and Niyikiza I. Based on Calvert and Niyikiza I, a POSA

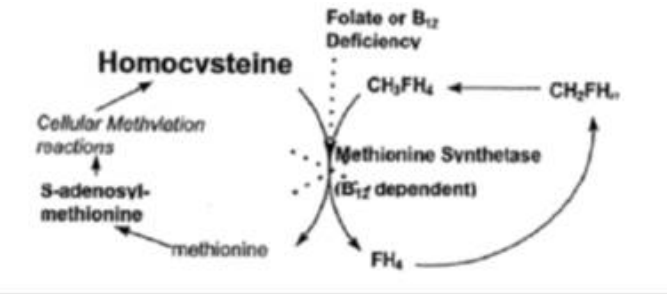
would have added vitamin B_{12} to the folic acid pretreatment regimens of Worzalla and Hammond I to arrive at the claimed invention.

A primary motivation for adding vitamin B_{12} would have been to decrease pemetrexed-related toxicity:

- As taught by Niyikiza I, "[e]levated baseline homocysteine levels (≥10 μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA [pemetrexed]." Ex. 1006, Niyikiza I at 127.
- Calvert summarizes Niyikiza's finding that elevated homocysteine predicts pemetrexed toxicity and further explains that "any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine." Ex. 1007, Calvert at 8 (citations omitted). Thus, a POSA would recognize that the elevated homocysteine levels described in Niyikiza are due to a folic acid and/or vitamin B_{12} deficiency.
- It was also well-known that elevated homocysteine levels should be lowered by administering folic acid with vitamin B_{12}. *See*, e.g., Ex. 1020, Brattström, Abstract; Ex. 1004, Schiff Decl. ¶¶ 74-79.

Based upon Niyikiza's teaching of a correlation between elevated homocysteine levels and pemetrexed toxicity and Calvert's teaching that those elevated homocysteine levels are caused by a folic acid and/or vitamin B_{12} deficiency, a POSA would have been highly motivated to add vitamin B_{12} to the folic acid pretreatment regimen of Worzalla and Hammond I. By pretreating with both folic acid and vitamin B_{12}, a POSA would address the underlying cause for the elevated homocysteine levels (a deficiency of folic acid, vitamin B_{12}, or both) and thus would reasonably expect that this pretreatment regimen would reduce the severity or prevalence of pemetrexed's toxicity. Ex. 1004, Schiff Decl. ¶¶ 66-79.

The POSA's knowledge that vitamin B_{12} is necessary for cells to convert folic acid into a useful derivative would have provided additional motivation to administer vitamin B_{12}. Specifically, it was known in the 1990s that vitamin B_{12} was necessary to convert the folic acid derivative 5 methyl tetrahydrofolate ("CH_3FH_4") into tetrahydrofolate or tetrahydrofolic acid ("THF" or "FH_4"). Cells cannot process CH_3FH_4, and thus, it is useless in DNA synthesis. Ex. 1004, Schiff Decl. ¶ 72. By contrast, the converted form ("FH4") can be used by a number of other enzymes in DNA synthesis. As shown in the reproduction of Figure 8 of Calvert below, CH_3FH_4 is converted to FH_4 by methionine synthase.



The conversion reaction is accomplished by removing the methyl group from CH_3FH_4 and adding it to homocysteine to make methionine. As explained in Calvert, it was known that methionine synthase requires vitamin B_{12} as a substrate in order to operate. Ex. 1004, Schiff Decl. ¶ 73. Thus, vitamin B_{12} was known as a cofactor necessary for folate metabolism. Accordingly, a POSA would have recognized that homocysteine levels are reduced only when both folic acid and vitamin B_{12} are present in sufficient amounts.

A POSA would have also wanted to protect against overlooking a vitamin B_{12} deficiency. Ex. 1004, Schiff Decl. ¶¶ 83-86. It was "well known" that it was "inappropriate" to treat "Cbl [cobalamin] deficiency with large doses of folic acid" because it could result in overlooking a hematologic response and deterioration of neurologic function – sometimes call B_{12}-deficiency "masking." Ex. 1050, Allen at 95. Thus, as noted in the '126 Patent, when administering folic acid, "the inclusion of B_{12} will be useful as a safeguard for patients misdiagnosed as folate deficient, even though they are actually B_{12} deficient, since treatment with folate

alone in such patients is extremely dangerous." Ex. 1018, '126 Patent at 7:51-54; see Ex. 1039, Ubbink I at 1931; Ex. 1004, Schiff Decl. ¶¶ 83-84.

To the extent Lilly attempts to undermine Niyikiza I by arguing that an earlier abstract, Niyikiza II, did not directly observe a correlation between pemetrexed toxicity and elevated MMA levels, which would indicate a vitamin B_{12} deficiency, the lack of such observation does not mean such a correlation does not exist. Ex. 1006, Niyikiza I; Ex. 1016, Niyikiza II. Because homocysteine and MMA are themselves highly correlated to one another, especially in patients with vitamin B_{12} deficiencies, they may not be discerned as separate variables correlated with the outcome of pemetrexed toxicity. Ex. 1004, Schiff Decl. ¶ 80. Regardless of the lack of an observed correlation between toxicity and MMA levels, in light of Calvert, the POSA would have erred on the side of adding vitamin B_{12}, an otherwise innocuous vitamin, to the folic acid pretreatment regimen of Worzalla and Hammond I. Ex. 1020, Brattström at Abstract; Ex. 1018, '126 patent at 7:51-54; Ex. 1004, Schiff Decl. ¶¶ 80-86.

At a minimum, the teachings of Niyikiza I and Calvert would have motivated the POSA to at least test patients for elevated homocysteine, and for those patients with elevated homocysteine levels, to test them for both folic acid and vitamin B_{12} deficiencies prior to starting pemetrexed therapy. Ex. 1004, Schiff Decl. ¶ 87. With respect to at least those patients with a confirmed deficiency of

both folic acid and vitamin B_{12}, the POSA would have been motivated to add vitamin B_{12} to the pretreatment regimens of Worzalla and Hammond I. *Id.* ¶¶ 87-90. Even if a POSA would have been motivated to pretreat only this subpopulation of patients, the claims of the '209 Patent, which cover this subset of patients, are invalid. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300-01 (Fed. Cir. 2007) (if the species is obvious then the genus is obvious as well); *see also Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 623 (Fed. Cir. 1995) (holding that a claimed method need be performed "sometimes, but not always" to meet the claim).

b. The Prior Art Taught Combining Antifolates with Vitamin B_{12} and Folic Acid

Several prior art references expressly disclose treating cancer patients taking antifolates with both vitamin B_{12} and folic acid. For example, Carrasco reports a patient suffering from leukemia that was treated with the antifolate methotrexate. The methotrexate resulted in toxicities that were ameliorated by, inter alia, 2 mg/day of vitamin B_{12} and 5 mg/day folic acid. Ex. 1032, Carrasco at 767-68. European Patent Application No. 0595005 ("EP005") discloses that vitamin B_{12} may lower homocysteine levels resulting from "any known cause" and that such causes include drugs such as the antifolate methotrexate. Ex. 1033, EP005 at 4. Providing patients with these vitamins before taking the antifolate was a small and

obvious step, particularly in light of Niyikiza I and Calvert's teaching of the link between pemetrexed toxicity and baseline homocysteine levels. Ex. 1006, Niyikiza I at 127; Ex. 1007, Calvert at 8-9; Ex. 1004, Schiff Decl. ¶¶ 66-79.

Likewise, the text "Antifolate Drugs in Cancer Therapy" not only explains the rationale behind administering folic acid in conjunction with antifolates generally, but also suggests that adequate levels of vitamin B_{12} may have a significant effect on toxicity:

> [D]ietary supplementation with folic acid may "normalize" the dose response for achieving antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues having low folate requirements, without meeting the high folate demands of rapidly dividing tumor cells.
>
> The biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins B_{12} and B_6. Thus, the status of all three vitamins in patients may significantly influence the severity or toxicity observed during chemotherapy.

Ex. 1012, Mendelsohn at 270. Thus, supplementation of both folic acid and vitamin B_{12} to ameliorate antifolate toxicity was known in the prior art.

At minimum, a POSA would have recognized that these prior art teachings indicate a reasonable expectation of success in achieving efficacy and acceptable toxicity for pemetrexed with the administration of both folic acid and vitamin B_{12}.

2. Claims 1 and 2 Are Obvious Over Calvert and Niyikiza I in View of Worzalla or Hammond I, and a POSA's Knowledge of the Relationship between Homocysteine, Folic Acid and Vitamin B_{12}

Claim 1 of the '209 Patent is directed to a method for administering pemetrexed to a patient in need thereof comprising administering effective amounts of folic acid and a MMA lowering agent followed by administering an effective amount of pemetrexed. Claim 2 specifies that the MMA lowering agent is vitamin B_{12}. The claimed "effective amount" requires only that the amounts of folic acid and MMA lowering agent (*e.g.*, vitamin B_{12}) must be capable of reducing the prevalence or severity of one or more toxicities associated with pemetrexed. *See* Ex. 1035, Joint Claim Construction Statement at 1.

As noted in the claim chart below, Worzalla and Hammond I teach each limitation of claims 1 and 2, except the step of administering a MMA lowering agent (*e.g.*, vitamin B_{12}). However, as previously noted, a POSA would have been motivated to add vitamin B_{12} to the pretreatment of regimens of Worzalla and Hammond I based upon the teachings of Calvert and Niyikiza I. *See* Section VI.F.1, supra, at 27. Specifically, Calvert's review article explains that "pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA." Ex. 1007, Calvert at 9 (citing Niyikiza II). Niyikiza I details how these "[e]levated baseline homocysteine levels (≥ 10 μM) highly correlate with severe hematologic and nonhematologic toxicities following

treatment with MTA *[i.e.*, pemetrexed]." Ex. 1006, Niyikiza I at 127. Calvert further explains that elevated homocysteine levels can be caused by a deficiency of ***both*** folic acid and vitamin B_{12}. Ex. 1007, Calvert at 8. The POSA also would have been aware that administering a combination of folic acid and vitamin B_{12} lowers elevated homocysteine levels. *E.g.*, Ex. 1020, Brattström at Abstract; Ex. 1039, Ubbink I at 1931; Ex. 1040, Brönstrup at Abstract; Ex. 1041, Ubbink II at 321. As such, a POSA would have been motivated to add vitamin B_{12} to the folic acid pretreatment regimens of Worzalla and Hammond I. The reasonably expected result: the normalization of elevated baseline homocysteine levels and a corresponding reduction in the prevalence or severity of pemetrexed toxicity. Ex. 1004, Schiff Decl. ¶ 90.

The claim chart below identifies where in the prior art each of the claimed limitations are found.

Claims of the '209 Patent	Prior Art
1[a]. A method for administering pemetrexed disodium to a patient in need thereof comprising	**Worzalla (Ex. 1013)**: "LY231514 produced potent antitumor activity against the L5178Y/TK-/HX- lymphoma at 100-fold lower dose levels . . . in [low folate diet] mice . . . ." *Id.* at 3238. "The disodium salt of LY231514 was synthesized at Eli Lilly and Co." *Id.* at 3235. or **Hammond I (Ex. 1015)**: "A phase I and

Claims of the '209 Patent	Prior Art
	pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)." *Id.* at Title.
[b] administering an effective amount of folic acid and	**Worzalla (Ex. 1013)**: "Folic acid supplementation was demonstrated to preserve the antitumor activity of [pemetrexed] while reducing toxicity." Ex. 1013, Worzalla at 3235 (abstract). "Mice maintained on [low folate diet] LFD for two weeks before intraperitoneal administration of LY231514 daily for 10 days . . . ." *Id.* at 3236. "For mice on LFD that received a folate supplement of 15 mg/kg/day via oral gavage, significant inhibition of tumor growth was noted . . . ." *Id.* at 3237. **or** **Hammond I (Ex. 1015)**: ". . . FA acid (5 mg/day) for 5 days starting 2 days before MTA [pemetrexed] . . . ." "Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity."
[c] an effective amount of a methylmalonic acid lowering agent	**Niyikiza I (Ex. 1006)**: "Toxicities resulting from treatment with MTA [pemetrexed] appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥ 10 μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with

Claims of the '209 Patent	Prior Art
	MTA." **Calvert (Ex. 1007)**: "Thus, any functional deficiency either in B_{12} or folate will result in . . . a consequent increase in the plasma level of homocysteine (Fig. 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA." *Id.* at 8-9 (endnotes omitted). **and optionally** **Brattström (Ex. 1020)**: "Supplementation with a combination of folic acid and cyanocobalamin [*i.e.*, vitamin B_{12}] will secure full homocysteine-lowering effect . . . ." *Id.* at Abstract. **Ubbink I (Ex. 1039)**: "It is therefore essential that vitamin B-12 and folate be combined to treat hyperhomocysteinemia." *Id.* at 1931. **Brönstrup (Ex. 1040)**: "[V]itamin B-12 may be beneficial when included in supplements or in a food-fortification regimen together with folic acid." *Id.* at Abstract. **Ubbink II (Ex. 1041)**: "Although folic acid is the most powerful [total homocysteine] tHcy- lowering agent, this does not imply that vitamin B_{12} and vitamin B6 may be omitted in the treatment of moderate hyperhomocyst(e)inemia. Vitamin B_{12}

Claims of the '209 Patent	Prior Art
	supplementation has a small, but significant effect on circulating tHcy concentrations . . . ." *Id.* at 321.
[d] followed by administering an effective amount of pemetrexed	**Worzalla (Ex. 1013)**: "Folic acid supplementation was demonstrated to preserve the antitumor activity of [pemetrexed] while reducing toxicity . . . ." Ex. 1013, Worzalla at 3235 (Abstract). "Mice maintained on [low folate diet] LFD for two weeks before intraperitoneal administration of LY231514 daily for 10 days . . . ." *Id.* At 3236. **or** **Hammond I (Ex. 1015)**: "As preclinical evaluations indicate that FA supplementation increases the therapeutic index of MTA [pemetrexed] . . . ." "Methods: . . . FA acid (5 mg/day) for 5 days starting 2 days before MTA [pemetrexed] at 600, 700, 800[,] 925 mg/m2." *Id.*
[e] the methylmalonic acid lowering agent is selected from the group consisting of vitamin B_{12}, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.	**Niyikiza I (Ex. 1006)**: "Toxicities resulting from treatment with MTA [*i.e.*, pemetrexed] appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels ($\geq$ 10 μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with

Claims of the '209 Patent	Prior Art
	MTA." **Calvert (Ex. 1007)**: "Thus, any functional deficiency either in B_{12} or folate will result in . . . a consequent increase in the plasma level of homocysteine (Fig. 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA." *Id.* at 8-9 (endnotes omitted). **and optionally** **Brattström (Ex. 1020)**: "Supplementation with a combination of folic acid and cyanocobalamin [*i.e.*, vitamin B_{12}] will secure full homocysteine-lowering effect and prevent occurrence of vitamin B-12 deficiency during the course of therapy." *Id.* at Abstract. **Ubbink I (Ex. 1039)**: "It is therefore essential that vitamin B-12 and folate be combined to treat hyperhomocysteinemia." *Id.* at 1931. **Brönstrup (Ex. 1040)**: "[V]itamin B-12 may be beneficial when included in supplements or in a food-fortification regimen together with folic acid." *Id.* at Abstract. **Ubbink II (Ex. 1041)**: "Although folic acid is the most powerful [total homocysteine] tHcy- lowering agent, this does not imply that vitamin B_{12} and vitamin B6 may be omitted in the

Claims of the '209 Patent	Prior Art
	treatment of moderate hyperhomocyst(e)inemia. Vitamin B_{12} supplementation has a small, but significant effect on circulating tHcy concentrations . . . ." *Id.* at 321.
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B_{12}.	*See* 1[e] above.

a. The POSA Would Have Had a Reasonable Expectation of Success

Obviousness requires a reasonable expectation of success in practicing the claimed method, not absolute predictability. *In re Droge*, 695 F.3d 1334, 1338 (Fed. Cir. 2012). In view of the prior art, a POSA would have had a reasonable expectation that pretreating a patient with folic acid and vitamin B_{12} would reduce toxicity of pemetrexed while also providing a therapeutic benefit in at least some patients. Ex. 1004, Schiff Decl. ¶ 90.

Both Worzalla and Hammond I teach that folic acid pretreatment reduces toxicity while providing a therapeutic benefit. Worzalla reported that "[f]olic acid supplementation was demonstrated to preserve the antitumor activity of [pemetrexed] while reducing toxicity." Ex. 1013, Worzalla at 3235 (Abstract). Hammond I taught that pretreating with folic acid "ameliorat[es]" toxicity while increasing "the therapeutic index of MTA [pemetrexed] . . . ." Ex. 1015, Hammond

I. Hammond II further notes that folic acid pretreatment with the regimens disclosed in Hammond I resulted in a partial response in a patient with metastatic colon cancer. Ex. 1014, Hammond II. Thus, while the studies described in the Hammond abstracts were designed to address toxicity only, Hammond II makes preliminary observations with respect to efficacy. Consistent with the teachings of Worzalla and the Hammond abstracts, Lilly's prior art '974 Patent confirms that folic acid pretreatment reduces toxicity without destroying the therapeutic benefits of antifolates, including pemetrexed. Ex. 1005, '974 patent at 1:47-58, 3:1-22 (formula).[5]

Moreover, the mouse model described in Worzalla supports a reasonable expectation of at least some efficacy in humans, even if the Board narrowly construes "patients" to mean humans.[6] Ex. 1013, Worzalla at Abstract. Indeed,

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[5] Lilly dispelled any question as to whether the prior art '974 Patent covers pemetrexed when it listed the patent in the Orange Book in connection with pemetrexed, thus admitting that the '974 Patent's teachings regarding pretreating patients with folic acid before administering an antifolate apply to pemetrexed. Ex. 1025, Orange Book Listing for Alimta® at 1025-0004.

[6] Worzalla acknowledged that prior studies showed "poor predictive value of mouse models for antifolate toxicity . . . partially due to the fact that standard

the '209 Patent relies on a mouse model similar to the one disclosed in Worzalla as allegedly supporting the benefits of pretreating the claimed "patient" with folic acid and vitamin B_{12} before starting pemetrexed therapy. Compare Ex. 1013, Worzalla at 3236, with Ex. 1001, '209 patent, 8:4-9.

The viability of animal studies as predictors of toxicity and efficacy is further confirmed by FDA guidance. At least as early as 1996, FDA has stated that "[a]cute toxicity studies in animals are usually necessary for any pharmaceutical intended for human use." Ex. 1048, FDA Single Dose Guidance at 1 (emphasis added). The FDA also has published guidance counseling on how "effective and nontoxic dose findings" for animals should be presented so that their relevancy to proposed human dosing may be considered. Ex. 1049, FDA E6 Guidance at 45. More recently, the FDA published guidance on its "Animal Rule" for granting marketing approval based on animal efficacy studies under some circumstances. Ex. 1046, FDA Animal Rule Guidance at 2. Even if mouse studies alone were not sufficient, the Hammond abstracts involved phase I studies in humans. Ex. 1015, Hammond I; Ex. 1014, Hammond II. Thus, regardless of the Board's construction

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laboratory mouse diets contain high levels of folic acid." Ex. 1013, Worzalla at 3237. Worzalla overcame this shortcoming in prior studies by feeding two groups of mice a folic acid-deficient diet. *Id.* at 3236.

of "patient," a POSA would have had a reasonable expectation that pretreating with folic acid and vitamin B_{12} would reduce pemetrexed toxicity while preserving at least some antitumor efficacy in mammals generally, and humans, specifically. Ex. 1013, Worzalla, Abstract; Ex. 1015, Hammond I; Ex. 1014, Hammond II.

Numerous references suggesting that vitamin B_{12} may have anti-tumor effects would have given the POSA an additional reason to expect success in treating cancer patients by adding vitamin B_{12} to Hammond I and Worzalla's pemetrexed and folic acid pretreatment. *E.g.*, Ex. 1023, Arsenyan; Ex. 1026, Sofyina, Ex. 1027, Herbert, Ex. 1028, Tisman. For example, Arsenyan shows that when vitamin B_{12} was administered, either before or contemporaneously with the antifolate methotrexate, the mice had an increase in survival notwithstanding an initial transient increase in tumor size. Ex. 1023, Arsenyan at 1300 (showing 21% increase in lifetime of animals pretreated with vitamin B_{12} and methotrexate). Ex. 1004, Schiff Decl. ¶ 88. The same group published a second study in 1979 reporting additional tests showing a "possible increase of the antitumor effect of MTX [methotrexate] with the use of methylcobalamine analogs and methionine synthase inhibitor." Ex. 1026, Sofyina at 7. Similarly, other studies "confirmed that both folinic acid and folic acid can potentiate 5FU activity against different tumor cells." Ex. 1028, Tisman, Abstract.

These references supply yet another reason for a POSA to expect success in combining antifolate treatment with vitamin B_{12}. Consistent with the teachings of Arsenyan, which taught a transient increase in tumor size resulted in increased survival, a POSA would have understood that

> [f]olic acid and vitamin B_{12} can prove useful in those tumors that grow more rapidly as more of these vitamins are supplied, because the tumor cells can be stimulated into the DNA synthesis phase in which a number of cancer chemotherapy agents exert their deadly effects.

Ex. 1027, Herbert at 301. In light of the foregoing, it was known that chemotherapy agents "c[ould] be used in a sequence ***right after*** folic acid and/or vitamin B_{12}." *Id.* (emphasis added); *see also* Ex. 1028, Tisman, Abstract. Thus, the POSA would have reasonably expected that vitamin B_{12} pretreatment to have beneficial antitumor effects.

To the extent Lilly attempts to argue that Arsenyan's suggestion that vitamin B_{12} caused temporary tumor growth is a teaching away, such an argument is flawed because it ignores the teachings of the prior art "viewed as a whole." *See Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1166 (Fed. Cir. 2006). If anything, the prior art's teachings that combining antifolates with vitamin B_{12} resulted in a reduction in long-term tumor growth and an increase in survivability provide yet another reason why a POSA would add vitamin B_{12} to the folic acid pretreatment regimen of Worzalla and Hammond I. *See* Ex. 1004, Schiff Decl. ¶¶ 88-90.

Moreover, Lilly itself apparently argued during the process of obtaining FDA approval for pemetrexed that "[f]or vitamin B_{12}, literature searches found no evidence for stimulation of tumor growth by this vitamin." Ex. 1036, Teva Litigation Trial Tr. 1278:12-21 (Chabner Cross).

b. No Secondary Considerations Support Non-Obviousness

To overcome Petitioner's strong showing of prima facie obviousness, the Patent Owner has the burden of establishing any secondary considerations of alleged non-obviousness. Although secondary considerations must be taken into account, they do not control the analysis where, as here, there is an otherwise strong case of obviousness. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Petitioner reserves the right to supplement its position regarding secondary considerations in response to any allegations the Patent Owner may raise in this proceeding.

The Patent Owner may point to correspondence with the FDA during the regulatory approval process as evidence of alleged skepticism. But this FDA correspondence appears to demonstrate just the opposite. As an initial matter, this correspondence was filed under seal in the Teva Litigation and thus Petitioner does not currently have access to it. As best Petitioner can ascertain, the FDA requested the Patent Owner to provide the rationale for adding a folic acid/vitamin B_{12} pretreatment regimen to the clinical trials of pemetrexed. Lilly apparently

responded to the FDA's requests by affirmatively representing that "[e]xternal consultants, including an expert in folate metabolism, were in agreement that this amount of [added] folic acid should be effective in reducing homocysteine levels, but these low levels should not be detrimental to efficacy" and that "experts felt that supplementation with low levels of folic acid would not adversely affect efficacy of pemetrexed." Ex. 1036, Teva Litigation Trial Tr. 808:6-810:10 (Niyikiza direct), 874:16-876:25 (Niyikiza cross). Lilly cannot have it both ways – experts cannot both be "in agreement" that vitamin pretreatment is expected to be efficacious when Lilly is seeking approval but skeptical that a POSA would expect vitamin pretreatment would work when its patent is later challenged as obvious.

To the extent that the FDA indicated that adding a folic acid and vitamin B_{12} pretreatment regimen was at the Patent Owner's risk, this type of alleged "skepticism" is legally irrelevant because it merely reflects the fact that the FDA was performing its duties of ensuring the safety and efficacy of treatments under regulatory review. *See Bayer Healthcare Pharm., Inc. v. Watson Pharm. Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (holding no skepticism shown because FDA request for clinical safety data "reflects attention to the FDA's normal duties ensuring the safety and efficacy of new drugs by requiring actual data to corroborate statements in a new drug application"); *Tyco Healthcare Grp. LP v. Mut. Pharm. Co. Inc.*, 642 F.3d 1370, 1377 (Fed. Cir. 2011) (rejecting FDA

correspondence as evidence of skepticism when FDA asked the patentee to "provide [a] rationale" for the claimed method of use); *Dow Jones & Co., Inc. v. Ablaise Ltd.*, 606 F.3d 1338, 1352 (Fed. Cir. 2010) (rejecting evidence that "d[id] not directly address whether there was actual skepticism concerning the invention . . .").

Further, based on the documentation available to Petitioner, it appears that the purported FDA skepticism was rooted in concerns over Lilly changing its experimental protocol relatively late in the FDA approval process. FDA regulations set strict requirements for amending the protocols for clinical investigations. *See* 21 C.F.R. § 312.30(b). Here, Lilly apparently revised its protocol without following all the guidelines and thus did so at its own risk.

Nor do any post-priority date statements by either the FDA or "experts" that the Patent Owner may offer provide legally relevant evidence of alleged skepticism. *See*, *e.g., Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 679-80 (D. Del. 2013) (rejecting testimony of skepticism where expert "never published anything documenting this initial skepticism" and patent owner "did not produce any literature expressing initial skepticism . . . ."); *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp.2d 427, 456-57 (D. Del. 2010) (rejecting post-priority date statement by "accomplished researcher" as evidence of skepticism), aff'd in relevant part, 694 F.3d 1344, 1357-58 (Fed. Cir. 2012).

The Patent Owner may also contend that the claimed invention achieved "unexpected results." That argument is also without merit. Rather than being "unexpected," the results were reasonably expected. Worzalla and Hammond I taught folic acid pretreatment with pemetrexed. For the reasons explained above, a POSA would have been motivated to add vitamin B_{12} to the folic acid pretreatment regimens of Worzalla and Hammond I. The reasonably expected result: a reduction in the severity and/or prevalence of toxicity while providing antitumor efficacy associated with pemetrexed in at least some patients.

Nor is there a nexus between any alleged commercial success and the invention claimed in the '209 Patent. Lilly listed its '974 and '932 patents, which claim, respectively, folic acid pretreatment with an antifolate such as pemetrexed (Ex. 1005, '974 patent, 8:60-10:36) and the compound pemetrexed specifically (Ex. 1034, '932 patent, 20:27-22:11), in the FDA's Approved Drug Products with Therapeutic Equivalents Evaluations ("Orange Book") for Alimta®. Until the expiration of its associated exclusivity on July 2, 2012, the prior art '974 patent served, and the '932 patent continues to serve, as strong financial disincentives for others to develop a product involving folic acid/vitamin B_{12} pretreatment with pemetrexed. Ex. 1025, OB listing for Alimta®. *See*, *e.g., Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

c. The Patent Owner's "Teaching Away" Arguments Lack Merit

Contrary to the express teachings of the prior art, the Patent Owner may argue that the prior art "teaches away" from folic acid and/or vitamin B_{12} pretreatment because of alleged concerns that this pretreatment regimen would eliminate pemetrexed's antitumor efficacy. That argument is factually and legally without merit, and belies Patent Owner's contemporaneous conduct.

To "teach away," a prior art reference must "criticize, discredit, or otherwise discourage" the use of folic acid supplementation with pemetrexed. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Even a "statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). The prior art does not criticize, discredit, or otherwise discourage pretreating with folic acid. To the contrary, Lilly's own prior art (*i.e.*, the Hammond abstracts, the Worzalla article, and the '974 Patent) expressly teaches that folic acid pretreatment reduced pemetrexed toxicity while preserving antitumor efficacy. *See* Ex. 1004, Schiff Decl. ¶¶ 53-63; Ex. 1013, Worzalla at Abstract ("Folic acid supplementation was demonstrated to preserve the antitumor activity of [pemetrexed] while reducing toxicity."); Ex. 1015, Hammond I (folic acid pretreatment "ameliorat[es]" toxicity while improving pemetrexed's therapeutic index); Ex. 1005, '974 Patent at 1:47-58, 5:31-48, 6:51-

56, 10:12-21 (Antifolates such as pemetrexed, can be administered with folic acid pretreatment to reduce toxicity "without affecting the therapeutic efficacy."). Indeed, subsequent studies have cited Worzalla as demonstrating that "nutritional folic acid (FA) supplementation preserved the antitumor activity of pemetrexed while dramatically reducing toxicity." Ex. 1037, Bajetta at 1543, 1547.

Lilly may nonetheless attempt to manufacture a "teaching away" by comparing Hammond I or II, which involved treating patients with folic acid, with another phase I study that involved treating patients with pemetrexed alone. Any such effort is without merit for several reasons. First, phase I studies are not intended to measure a drug's efficacy. Thus, the Patent Owner's comparison is a non-starter. A POSA would not compare phase I studies in order to draw conclusions about the comparative efficacy of pemetrexed (with and without folic acid pretreatment). Ex. 1004, Schiff Decl. ¶ 56. Second, Patent Owner's argument also ignores the express teachings of the art, which state that folic acid pretreatment does not affect therapeutic efficacy. Third, it also ignores what the claims actually require. The claims merely require some therapeutic benefit; they do not require that the claimed pemetrexed treatment program have the same antitumor efficacy as pemetrexed administered alone.

Fourth, even ***if*** the claimed invention presented the POSA with an allegedly less preferred option (reduced toxicity at the expense of potentially reduced

antitumor efficacy), that is not a teaching away. *See* Syntex, 407 F.3d at 1379-80 ("A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination."). Both approaches (pemetrexed alone or pemetrexed with folic acid/vitamin B_{12} pretreatment) were taught by the prior art, and a POSA would have simply balanced the known benefits and risks in determining how to proceed with respect to a given patient. *See* Ex. 1004, Schiff Decl. ¶ 86; *see Medichem S.A.*, 437 F.3d at 1166-67 (declining to find a teaching away based on tertiary amines' "potential disadvantages" because the prior art "viewed as a whole" indicated that the "addition of a tertiary amine sometimes works to improve the yield . . . especially when a tertiary amine is used in relatively low concentrations" (emphasis in original)).

In short, even ***if*** the Patent Owner can muster isolated snippets from the prior art to the contrary, the teachings of Calvert, Niyikiza I and the other art cited herein provided strong motivation for adding vitamin B_{12} to the folic acid pretreatment regimens of Worzalla and Hammond I. *See In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991) (if there is a conflict as to what path would be productive, the court "must weigh each reference for its power to suggest solutions to an artisan of ordinary skill.").

3. Claims 3-10, 12, and 14-21 Are Obvious in Further View of the Known Dosages and Schedules for Administering Folic Acid and Vitamin B_{12}

The claimed folic acid and vitamin B_{12} dosages and schedules of claims 3-10, 12, and 14-21 are typical of those described in the prior art and would have been within the knowledge of the POSA. Accordingly, the limitations of claims 3-10, 12, and 14-21 requiring specific dosages of folic acid, specific dosages of vitamin B_{12}, and/or specific dosing schedules add nothing patentable and these claims are likewise obvious over the prior art.

Numerous references taught pretreatment dosages of folic acid within a 350 μg to 600 μg range – the narrowest range of folic acid dosages required by the '209 Patent claims. Ex. 1001, '209 Patent, claims 10, 18. For example, Lilly's prior art '974 Patent described a clinical study in which a patient undergoing therapy with the antifolate lometrexol received 0.5 to 1.0 mg/day of folic acid, and that under this dosing regimen, lometrexol was well tolerated for up to 12 months of therapy. Ex. 1005, '974 Patent at 8:49-56. This study supported the claims of the patent that Lilly listed in the Orange Book as covering the pretreatment of folic acid and vitamin B_{12} prior to administration of pemetrexed. *See*, *e.g.*, Ex. 1005, '974 Patent, claim 20. Other prior art concluded that when treating "patients with other micronutrient deficiencies" with the antifolate methotrexate, "the intake of one multiple-vitamin pill containing 900 nmol of folic acid (400 μg/day) may also

modulate [the] toxicity" of methotrexate. Ex. 1010, Morgan at 838; Ex. 1004, Schiff Decl. ¶¶ 91-99. The '126 Patent also taught treating folic acid deficiencies with oral doses of folic acid supplements in the range of 400-1000 μg. *See*, *e.g.*, Ex. 1018, '126 Patent at 7:3-32.

To the extent Lilly attempts to undermine the teachings of the Hammond abstracts by pointing to the Hammond abstracts' use relatively high pretreatment doses of folic acid (5 mg), such argument does not undercut the prior art's suggestion of pairing standard pemetrexed dosages with lower doses of folic acid. A person of ordinary skill would recognize that the Hammond phase I study used very high dosages of folic acid because the pemetrexed doses tested likewise were "above the recommended phase II dose of [pemetrexed] alone." Ex. 1015, Hammond I at 620P. However, when using standard doses of pemetrexed, a POSA would have understood that the '974 Patent and Morgan suggested that lower doses of folic acid may reduce toxicity without reducing the anticancer activity of the antifolate.[7] Ex. 1005, '974 Patent at 8:43-56; Ex. 1010, Morgan at 836, 838; Ex. 1004, Schiff Decl. ¶¶ 98-99. Grindey also encouraged the use of low

[7] Lilly recognizes this point as it cites to another Morgan study in its Worzalla publication. Ex. 1013, Worzalla at 3239.

folic acid doses to ameliorate antifolate-related toxicity. Ex. 1011, Grindey at 1921 (Abstract).

Likewise, the claimed folic acid dosing schedules were known in the prior art – *i.e.*, dosing "1 to 3 weeks prior" or "1 to about 24 hours prior to" administering pemetrexed. Ex. 1001, '209 Patent, claims 6-7, 19-20. Hammond I and Worzalla taught folic acid pretreatment prior to initiating pemetrexed therapy. Ex. 1015, Hammond I at 620P (noting patients received "FA (5 mg/day) for 5 days starting 2 days before MTA . . . ."); Ex. 1013, Worzalla at 3236 (mice maintained on high folate diet for "two weeks before intraperitoneal administration of LY231514 daily"). Similarly, the '974 Patent taught folic pretreatment for periods of weeks prior to initiation of antifolate therapy. Ex. 1005, '974 Patent at 6:22-48. The '974 Patent also described folic acid pretreatment from about 1 to 24 hours prior to administration of the antifolate. *Id.* at 6:24-29. It was also known to administer folic acid on a daily basis. Ex. 1018, '126 Patent at 7:40-47.

With respect to the claimed vitamin B_{12} dosage amounts and schedules, the prior art taught that 1000 μg vitamin B_{12} was a standard intramuscular dose that could be administered every 6 to 12 weeks just as disclosed and claimed in the '209 patent. *See*, *e.g.*, Ex. 1019, Beutler at 302; Ex. 1001, '209 Patent, claims 4-5, 15, 21. The standard nature of this dosing regimen is further evidenced by the following: Ex. 1029, Kinloch at 99; Ex. 1030, Wray at 491; Ex. 1031, Tamura at

29. Indeed, the '209 Patent admits that intramuscular injections of vitamin B_{12} "are known in the art and are commercially available." Ex. 1001, '209 Patent at 5:15-18.

The claim chart below shows where each limitation of claims 3-10, 12, and 14-21 is taught in exemplary prior art.

Claims of the '209 Patent	Prior Art
3. The method of claim 2, wherein the vitamin B_{12} is administered as an intramuscular injection of about 500 µg to about 1500 µg.	**Beutler (Ex. 1019)**: "Stores of vitamin B_{12} can be replenished with 1000 µg of vitamin B_{12} injected daily or perhaps every other day for two weeks." *Id.* at 302. **Kinloch (Ex. 1029)**: "Injections of 1,000 µg. of vitamin B_{12} . . . given once every 12 weeks." *Id.* at 100. **Wray (Ex. 1030)**: disclosing a 1000 µg dose of vitamin B_{12} every two months. *Id.* at 491. **Tamura (Ex. 1031)**: "patients were treated with vit.B_{12} 1000 µg every 3 months as out-patients . . . ." *Id.* at 29.
4. The method of claim 2 [sic, 3], wherein the vitamin B_{12} is administered as an intramuscular injection of about 1000 µg.	*See* claim 3.
5. The method of claim 2, 3 or 4, wherein the vitamin B_{12} administration is repeated about every 6 to about every 12 weeks following the administration of vitamin B_{12} until the administration of the pemetrexed disodium is	**Beutler (Ex. 1019)**: "Two successful alternative maintenance programs are 1000 µg of hydroxocobalamin every two or three months . . . ." *Id.* at 302. **Kinloch (Ex. 1029)**: "Injections of

Claims of the '209 Patent	Prior Art
discontinued.	1,000 µg of vitamin B_{12} . . . given once every 12 weeks." *Id.* at 100. **Wray (Ex. 1030)**: disclosing a 1000 µg dose of vitamin B_{12} every two months. *Id.* at 491. **Tamura (Ex. 1031)**: "patients were treated with vit.B_{12} 1000 µg every 3 months as out-patients . . . ." *Id.* at 29.
6. The method of claim 5 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed sodium.	**'974 Patent (Ex. 1005)**: "As used in this invention, the term 'FBP binding agent' refers to folic acid . . . ." *Id.* at 5:12-13. ". . . FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment." *Id.* at 6:32-36.

Claims of the '209 Patent	Prior Art
7. The method of claim 5 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	**'974 Patent (Ex. 1005)**: "In the especially preferred embodiment of this invention, 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 lometrexol ... ." *Id.* at 6:37-41. **Hammond I (Ex. 1015)**: "So far, 33 minimally- and heavily- pretreated pts

Claims of the '209 Patent	Prior Art
	received 90 courses of FA [folic acid] (5 mg/day) for 5 days starting 2 days before MTA [pemetrexed] . . . ."
8. The method according to any one of claims 1-4, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	**Hammond I (Ex. 1015)**: "So far, 33 minimally-and heavily- pretreated pts received 90 courses of FA [folic acid] (5 mg/day) for 5 days starting 2 days before MTA [pemetrexed] . . . ." **'974 Patent (Ex. 1005)**: "In the especially preferred embodiment of this invention, 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 lometrexol . . . ." *Id.* at 6:37-41. **'126 Patent (Ex. 1018)**: "One embodiment of the present invention uses a non-prescription formulation comprised of between about 0.3-10 mg CN-cobalamin (B_{12}) and 0.1-0.4 mg folate . . . . Another embodiment of the present invention is comprised of a prescription formulation comprised of between about 0.3-10 mg B_{12} and 0.4-10.0 mg folate . . . ." *Id.* at 7:15-32.
9. The method of claim 8 wherein about 350 µg to about 1000 µg of folic acid is administered.	**'974 Patent (Ex. 1005)**: "In the especially preferred embodiment of this invention, 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 lometrexol . . . ." *Id.* at 6:37-41.

Claims of the '209 Patent	Prior Art
	'126 Patent (Ex. 1018): "One embodiment of the present invention uses a non-prescription formulation comprised of between about 0.3-10 mg CN-cobalamin (B_{12}) and 0.1-0.4 mg folate . . . . Another embodiment of the present invention is comprised of a prescription formulation comprised of between about 0.3-10 mg B_{12} and 0.4-10.0 mg folate . . . ." *Id.* at 7:15-32.

4. Claim 11 Is Obvious in Further View of the POSA's Knowledge of the Benefit of Combining Cisplatin with Pemetrexed

Several claims of the '209 Patent are directed to administering cisplatin in combination with pemetrexed disodium. Ex. 1001, '209 patent, claims 11, 13, 22. The POSA would have been aware of cisplatin, a chemotherapy drug that was first approved in 1978 and was frequently used to treat non-small cell lung cancer in combination with other agents. Ex. 1042, Sörenson at Abstract. Further, several prior art articles reported that cisplatin had shown promising results in combination with pemetrexed prior to 2000.

For example, Thödtmann I reported that "MTA [pemetrexed] may be safely combined with cisplatin" and that this schedule is "clinically active when both agents are administered on day 1 and that it should be pursued for further clinical development." Ex. 1017, Thödtmann I at 89 (Abstract), 92. Similarly, Thödtmann

III reports that the "combination of MTA and cisplatin shows encouraging antitumour activity." Ex. 1043, Thödtmann II at 618P. Both Thödtmann I and II are prior art under 35 U.S.C. § 102(a). Neither of these references is listed on the face of the patent as having been of record during prosecution of the '209 patent.

Calvert and Niyikiza I in combination with Worzalla or Hammond I taught folic acid and vitamin B_{12} pretreatment with pemetrexed. Thödtmann I and II further teach that co-administering pemetrexed and cisplatin is safe and clinically effective. Accordingly, it would have been obvious for a POSA to have combined these known treatment regimens for achieving the reasonably expected result of an antitumor therapeutic benefit while reducing the severity and/or prevalence of pemetrexed toxicity. Ex. 1004, Schiff Decl. ¶ 117-19.

The claim chart below shows where each element is disclosed in the prior art.

Claims of the '209 Patent	Prior Art
11. The method of claim 1 further comprising the administration of cisplatin to the patient.	*See* claim 1. **Thödtmann I (Ex. 1017)**: "MTA [pemetrexed] may be safely combined with cisplatin" and that this schedule is "clinically active." *Id.* at 89 (Abstract), 92. **Thödtmann II (Ex. 1043)**: "This combination of MTA and cisplatin shows encouraging antitumour activity."

Claims of the '209 Patent	Prior Art
	Id. at 618P.

5. Claims 13 and 22 Are Obvious over Worzalla or Hammond I in View of Niyikiza I, Calvert in Further View of the POSA's Knowledge of the Claimed Dosages, Schedules and Combination with Cisplatin

Claims 13 and 22 are directed to administering cisplatin to pemetrexed patients pretreated with folic acid and vitamin B_{12} according to prior art-recognized dosages and schedules, and are obvious for the same reasons applicable to claims 11, 12, and 21.

IX. CONCLUSION

For the foregoing reasons, Wockhardt 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 13,307 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 PURSUANT TO 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42**, including all exhibits were served on July 8, 2016, via Priority Mail Express® in its entirety on the following:

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