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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACCORD HEALTHCARE, INC., USA,
Petitioners

v.

Patent Owner of
U.S. Patent 7,772,209 to Niyikiza
Appl. No. 11/776,329 filed June 11, 2007
Issued Aug. 10, 2010

IPR Trial No. TBD

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,772,209 PURSUANT TO 35 U.S.C. § 312 AND 37 C.F.R. § 42.108

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OTHER AUTHORITIES

35 U.S.C. § 103……....*passim*

EXHIBIT LIST

Exhibit No.	Name	Referred To In The Petition As
Exhibit 1000:	Complaint - *Eli Lilly and Company v. Accord Healthcare, Inc., USA*, filed February 28, 2013 (1:13-cv-00335-TWP-DKL)	
Exhibit 1001:	U.S. Patent No. 7,772,209	("'209 Patent")
Exhibit 1002:	File History of U.S. Patent No. 7,772,209	
Exhibit 1003:	Carrasco et al., *Acute Megaloblastic Anemia: Homocysteine Levels Are Useful for Diagnosis and Follow-Up*, HAEMATOLOGICA, 84: 767- 768 (1999)	("Carrasco")
Exhibit 1004:	Hammond et al., *A Phase I and Pharmacokinetic (PK) Study of the Multitargeted Antifol (MTA) LY231514 with Folic Acid*, PROCEEDINGS OF AMERICAN SOCIETY OF CLINICAL ONCOLOGY, 17: Abs. No. 866 (1998)	("Hammond")
Exhibit 1005:	Calvert, *An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents*, SEMINARS IN ONCOLOGY, 26: 3-10 (1999)	("Calvert")
Exhibit 1006:	Niyikiza et al., LY231514 (MTA): *Relationship of Vitamin Metabolite Profile to Toxicity, American Society of Clinical Oncology*, PROCEEDINGS OF AMERICAN SOCIETY OF CLINICAL, 17: Abs. No. 2139 (1998)	("Niyikiza")
Exhibit 1007:	Malinow et al., *The Effects of Folic Acid Supplementation on Plasma Total Homocysteine Are Modulated by Multivitamin Use and*	("Malinow")

	Methylenetetrahydrofolate Reductase Genotypes, ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, 17: 1157-62 (1997)	
Exhibit 1008:	Refsum et al., *Clinical Significance of Pharmacological Modulation of Homocysteine Metabolism*, TRENDS IN PHARMACOLOGICAL SCIENCES, 11: 411-416 (1990)	("Refsum")
Exhibit 1009:	European Patent Application No. 0595005	("EP005")
Exhibit 1010:	Thodtmann et al., *Clinical and Pharmacokinetic Phase I Study of Multitargeted Antifolate (LY231514) in Combination with Cisplatin*, J. CLINICAL ONCOLOGY, 17: 3009-3016 (1999)	("Thodtmann")
Exhibit 1011:	Declaration of Dr. Peter Cole, M.D.	("Cole Declaration")
Exhibit 1012:	C.V. of Dr. Peter Cole, M.D.	

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, real party in interest, Accord Healthcare, Inc., USA ("Accord" or "Petitioner") respectfully requests *inter partes* review (IPR) of Claims 1-22 of U.S. Patent No. 7,772,209 ("the '209 Patent"), which was filed on July 11, 2007, and issued on August 19, 2010 to Clet Niyikiza and is currently assigned to Eli Lilly and Company ("Lilly" or "Patent or Owner").

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

A. REAL PARTY-IN-INTEREST UNDER 37 C.F.R. § 42.8(b)(1)

Petitioner Accord Healthcare, Inc., USA is the real party-in-interest for the instant petition.

B. RELATED MATTERS UNDER 37 C.F.R. § 42.8(b)(2)

The '209 Patent is asserted by the Patent Owner in the following litigations pending in the U.S. District Court for the Southern District of Indiana: *Eli Lilly and Company v. Accord Healthcare, Inc., USA*, filed February 28, 2013 (1:13-cv-00335-TWP-DKL) *see* Ex. 1000; *Eli Lilly and Company v. Accord Healthcare, Inc., USA, Apotex Inc. and Apotex Corp.*, filed against Accord on January 20, 2012 (1:12-cv-0086-TWP-DKL) and against Apotex Defendants on April 17, 2010 (12-cv-00499-TWP-DKL); *Eli Lilly and Company v. Teva Parental Medicines, Inc., et al.*, filed October 29, 2010 (1:10-cv-01376-TWP-DKL).

Petitioner is a party to two of these litigations. Petitioner is not aware of any pending prosecution concerning the '209 Patent.

C. LEAD AND BACK-UP COUNSEL

Petitioner provides the following designation of counsel.

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D. SERVICE INFORMATION

Please address all correspondence to the lead counsel at the address provided in Section I.C of this Petition. Petitioner also consents to electronic service by email at: accordipr@sughrue.com

II. PAYMENT OF FEES — 37 C.F.R. § 42.103

The Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 19-4880 for the fees set in 37 C.F.R. § 42.15(a) for this Petition for Inter Partes Review, and further authorizes payment for any additional fees to be charged to this Deposit Account.

III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. §§ 42.104

A. GROUNDS FOR STANDING UNDER 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.

The relevant statutory provision, 35 U.S.C. § 315(b), provides that "[a]n inter partes review may not be instituted if the petition requesting the proceeding is

filed more than 1 year after the date on which the petitioner…is served with a complaint alleging infringement of the patent."

Here, the Patent Owner served Accord with a complaint alleging infringement of the '209 Patent on or around February 28, 2013. This complaint related to Accord's Abbreviated New Drug Application (ANDA) for its 1000 mg/vial dosage form of pemetrexed.[1] Given that the Patent Owner served Accord with a complaint alleging infringement of the '209 Patent on or around February 28, 2013, this petition is being filed less than one year after the date on which Accord was served with "a complaint."

B. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.104(B) AND RELIEF REQUESTED

Petitioner requests inter partes review of claims 1-22 of the '209 Patent on the grounds set forth in the table below and requests that each of the claims be found unpatentable. An explanation of how claims 1-22 are unpatentable under the statutory grounds identified below, including the identification of where each element is found in the prior art references, and the relevance of each of the prior art references is provided in the form of detailed claim charts in section V below.

[1] In January 2012, Patent Owner commenced a lawsuit for infringement of the '209 Patent related to Accord's ANDA for its 100 mg/vial and 500mg/vial dosage form of pemetrexed. Although the two lawsuits name Accord, they involve entirely different products and are based on different set of facts.

Additional explanation and support for each ground of rejection is set forth in the Declaration of Dr. Peter Cole (Ex 11).

Ground	**'209 Patent Claims**	**Basis for Rejection**
Ground 1	Claims 1-10, 12, and 14-21	Obvious under 35 U.S.C. §103(a) over Hammond and Carrasco
Ground 2	Claims 1-10, 12, and 14-21	Obvious under 35 U.S.C. §103(a) over Calvert and Carrasco
Ground 3	Claims 1-10, 12, and 14-21	Obvious under 35 U.S.C. §103(a) over Niyikiza and EP005
Ground 4	Claims 1-10, 12, and 14-21	Obvious under 35 U.S.C. §103(a) over Niyikiza and Refsum
Ground 5	Claims 1-10, 12, and 14-21	Obvious under 35 U.S.C. §103(a) over Niyikiza and Malinow
Ground 6	Claims 11, 13, and 22	Obvious under 35 U.S.C. §103(a) over Calvert, Carrasco and Thodtmann

1. Effective filing dates

The earliest application to which the '209 Patent claims benefit is U.S. patent application No. 60/215,310 filed June 30, 2000.

2. Prior art

Carrasco was published in August 1999 and, therefore, is prior art at least under 35 U.S.C. §102(a)

Hammond was published in May 1998 and, therefore, is prior art at least under 35 U.S.C. § 102 (b)

Niyikiza was published in May 1998 and, therefore, is prior art at least under 35 U.S.C. § 102 (b)

Calvert was published in April 1999 and, therefore, is prior art at least under 35 U.S.C. §102 (b)

Refsum was published in October 1990 and, therefore, is prior art at least under 35 U.S.C. §102 (b)

Malinow was received in April 1996 and published in October 1996 and, therefore, is prior art at least under 35 U.S.C. §102 (b)

EP005 filed in September 1993 and published in May 1994 and, therefore, is prior art at least under 35 U.S.C. §102(b)

Thodtmann published in October 1999 and, therefore, is prior art at least under 35 U.S.C. §102(a)

C. CLAIM CONSTRUCTION UNDER 37 C.F.R. §§ 42.104(b)(3)

The claim terms in the '209 Patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. 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.

D. PERSON OF ORDINARY SKILL IN THE ART

The qualifications of a person of ordinary skill in the art to whom the '209 Patent is directed would be an MD with significant experience in the treatment of oncology patients, a significant understanding of antineoplastic agents including their efficacies, toxicities, safety, side effects, etc. Accord reserves the right to refine its POSA definition as additional information becomes available.

IV. SUMMARY OF THE '209 PATENT

The '209 Patent "relates to a method of administering an antifolate…in combination with a methylmalonic acid lowering acid and a FBP binding agent." Ex. 1001, '209 Patent, col. 3, lines 1-5. Folic acid is identified as a "preferred FBP binding agent." *Id*. at col. 3, lines 5-6. Vitamin B12 is described as a preferred example of the methylmalonic acid lowering agent. *Id.* at col. 4, lines 49-50.

The '209 Patent states that "life-threatening toxicity remains a major limitation to the optimal administration of antifolates" including aminopterin, methotrexate, lometrexel, and pemetrexed. *Id*. at col. 1, lines 11-61. The '209 Patent cites to several prior art references to note that the toxicity associated with antifolates is caused by increased homocysteine levels. *Id*. at col. 2, lines 14-31. The '209 Patent further states that the prior art taught supplementation with folic acid to lower homocysteine levels and thereby reduce cytotoxic activity caused by the antifolate drugs. *Id*.

Following this introduction, the patent specification turns to the alleged discovery underlying the '209 Patent, which is characterized as "a method for improving the therapeutic utility of antifolate drugs by administering" vitamin B12. *Id*. at col. 2, lines 32-40. The '209 Patent asserts that the alleged discovery was the reduction of toxicity by administration of a "methylmalonic acid lowering agent," such as vitamin B12, to a patient undergoing treatment. The '209 Patent also claims to 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 col. 2, lines 47-54.

Accordingly, the '209 patent further asserts that another alleged "discovery" was that administering a combination of folic acid and a methlymalonic acid lowering agent (such as vitamin B12) "synergistically reduces the toxic events associated" with antifolate drugs, and that this discovery was "unknown." *See id*. at col. 2, lines 47-50.

V. TECHNICAL BACKGROUND AND STATE OF THE ART

A. Antifolate Toxicity Linked to Elevated Homocysteine

As noted in the '209 Patent itself, toxicity was a major limitation to the admistration of antifolates, such as methotrexate and pemetrexed. *See* Ex. 1011, Cole Declaration at ¶ 31. It was known that the toxicity was precited by elevated homocysteine levels. *See* Ex. 1011, Cole Declaration at ¶ 31. In view of this

strong correlation between homocysteine levels and the occurrence of cytotoxic events caused by the administration of antifolates, those skilled in the art sought to reduce toxicity by lowering homocysteine levels. *See* Ex. 1011, Cole Declaration at ¶¶ 41-51.

B. Combination of Folic Acid and Vitamin B12 Lowers Homocysteine Levels

In order to understand why folic acid and vitamin B12 can be used to reduce the toxicity associated with pemetrexed, an understanding of the metabolism of intracellular homocysteine is important.

The metabolism of intracellular homocysteine was well known to one of ordinary skill in the art long before the filing of the application that issued as the '209 Patent. *See* Ex. 1011, Cole Declaration at ¶¶ 36-39. Publications such as Refsum, which was published in 1990, explain that only two pathways exist for metabolizing intracellular homocysteine: salvage to methionine through remethylation, or conversion to cysteine via the trans-sulfuration pathway. *See* Ex. 1011, Cole Declaration at ¶ 37. In most tissues, the former reaction is catalyzed by the enzyme methionine synthase This enzyme requires vitamin B12 as a cofactor and folic acid as a methyl donor cosubstrate. *See* Ex. 1011, Cole Declaration at ¶ 37.

In view of the finite number of identified routes of homocystiene metabolism (two), a person having ordinary skill in the art would know to focus on

methionine synthase. *See* Ex. 1011, Cole Declaration at ¶ 39. As discussed above, prior to the filing of the '209 Patent, a number of references disclosed the toxicity-reducing effects of folic acid, when co-administered with an antifolate. Only one enzyme involved in metabolism of homocysteine incorporates folic acid – methionine synthase. *See* Ex. 1011, Cole Declaration at ¶ 39. Methionine synthase also **requires** its cofactor, vitamin B12, to metabolize homocysteine. *See* Ex. 1011, Cole Declaration at ¶ 39. In view of this understanding, those skilled in the art supplemented the administration of antifolates with folic acid **and** vitamin B12 to reduce levels of homocysteine and, thereby, the resultant toxicity. *See* Ex. 1011, Cole Declaration at ¶¶ 39-41.

VI. PROPOSED REJECTIONS

A. GROUND 1: CLAIMS 1-10, 12, AND 14-21 ARE OBVIOUS IN VIEW OF CARRASCO AND HAMMOND

Claims 1-10, 12, and 14-21 of the '209 patent are obvious over Carrasco in view of Hammond. The claims of the '209 patent were allowed because the Examiner could not find any prior art disclosing a method of administering pemetrexed disodium to a patient in need that included "administration of a therapeutically effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent" (i.e., claims 1-10) or a method of administering pemetrexed to a patient in need, including administration of folic acid and vitamin B12 "prior to the first administration of pemetrexed disodium"

(i.e., claims 12, 14-21).

i. Scope and Content of Prior Art

a. Carrasco

Carrasco is a reference that the Examiner would have used to reject all the claims of the '209 Patent.

Carrasco discloses a study of a patient who is administered folic acid ***and*** vitamin B12 to ameliorate toxicity caused by the administration of the antifolate methotrexate. *See* Ex. 1003, Carrasco at 767. Specifically, following chemotherapy for leukemia, the patient was diagnosed with megaloblastic anemia and exhibited an elevated homocysteine level of 38 μmol/L (wherein the normal level is less than 16 μmol/L). *Id*. at 767-768; *see also* Ex. 1011, Cole Declaration at ¶ 42. Carrasco provides that "Vitamin B12 (cobalamin) and folic acid deficiencies lead to megaloblastic anemia (MA), and induce accumulation of methylmalonic acid (MMA) and homocysteine [HCY]." Ex. 1003, Carrasco at 767.

To lower the homocysteine levels and ameliorate the toxicity caused by the antifolate methotrexate, the patient was administered folinic acid (12 mg iv in one single dose), folic acid (5 mg/day for 14 days) and parenteral vitamin B12 (2 mg/day for 4 consecutive days). *Id*. at 768; *see also* Ex. 1011, Cole Declaration at ¶ 43. Carrasco reports that after 10 days of treatment "serum HCY [homocysteine] level decreased to normal value (9 μmol/L)." Ex. 1003, Carrasco at 768.

Carrasco is highly material to the validity of the '209 Patent claims because Carrasco discloses administering an effective amount of folic acid and methylmalonic acid lowering agent (vitamin B12) before, in conjunction with, and after administering the antifolate methotrexate to a patient in need thereof. *See id*. at 767-768.

While Carrasco does not disclose the order or exact amounts of folic acid and vitamin B12 administered; the '209 Patent concedes 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, '209 Patent, at col, 5, lines 37-41. This indicates that one of ordinary skill in the art would have arrived at the order, amount, duration, and manner of administering folic acid and vitamin B12 without undue experimentation. *See* Ex. 1011, Cole Declaration at ¶¶ 52-54.

b. Hammond

Hamond discloses that folic acid can be used to reduce the toxicity caused by pemetrexed. Specifically, Hammond reports on a Phase I study to determine whether administering folic acid before administering pemetrexed to human patients ameliorates toxicity and permits dose-escalation. *See* Ex. 1004, Hammond, at Abstract. In Hammond, twenty-one cancer patients were administered varying dose levels of pemetrexed and folic acid. *Id*. Hammond reports that

"administering folic acid 5 mg daily for 5 days starting 2 days before [beginning treatment with pemetrexed] reduces toxicity and permits dose escalation." *Id*.

ii. Claims 1-10, 12, and 14-21 are Obvious Over Carrasco and Hammond

A person of ordinary skill in the art would have been highly motivated to combine the teachings of Carrasco and Hammond to reduce toxicity caused by the antifolate pemetrexed. Ex. 1011, Cole Declaration at ¶ 64. As stated by the Supreme Court in *KSR v. Teleflex*, 127 S. Ct. 1727, 1740 (2007) "[i]f a person of ordinary skill can implement a predictable variation of the prior art in the manner claimed, § 103 likely bars its patentability." Given the statements in the '209 Patent that the industry was continually attempting to reduce toxicity associated with antifolates, such as pemetrexed, it would have been obvious for a person skilled in the art to combine Carrasco - which teaches that vitamin B12 can be administered along with folic acid in order to reduce the toxicity associated with an antifolate - with Hammond - which teaches that administering folic acid to patients before administering pemetrexed reduces the toxicity associated with the drug. Ex. 1011, Cole Declaration at ¶ 65. In other words, administering vitamin B12 and folic acid along with pemetrexed is obvious at least because it is a predictable variation of art that teaches administration of vitamin B12 and folic acid along with methotexate. Ex. 1011, Cole Declaration at ¶ 65.

The tables below show how each limitation of claims 1-10, 12 and 14-23 is taught by Carrasco and Hammond.

Claims of the '209 Patent	**Carrasco and Hammond**
1. A method for administering pemetrexed disodium to a patient in need thereof comprising	*See* Hammond (Abstract): Hammond discloses administering pemetrexed disodium to patients with solid cancers in phase I medical trials.
administering an effective amount of folic acid	*See* Hammond (Abstract): Hammond discloses that "administering folic acid 5 mg daily for 5 days starting 2 days before MTA [pemetrexed]" permits dose escalation.
and an effective amount of methylmalonic acid lowering agent	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days and **parenteral vitamin B12** 2 mg/day for 4 consecutive days" to reduce homocysteine levels and thereby ameliorate toxicity caused by the antifolate methotrexate. (Emphasis added) It would have been obvious to modify Hammond to administer vitamin B12 along with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration at ¶¶ 65-66.
followed by administering an effective amount of pemetrexed disodium, wherein	*See* Hammond (Abstract): Hammond discloses "administering folic acid 5 mg daily for 5 days starting 2 days ***before*** MTA [pemetrexed]." (Emphasis added). The order in which the vitamins are administered vis-à-vis the administration of pemeterxed is a matter of a physician's preference. Ex. 1011, Cole Declaration at ¶¶ 52-54. As a result, one skilled in the art would have arrived at the order in which the vitamins are administered without undue experimentation.
the methylmalonic acid lowering agent is selected from the group	*See* Carrasco (pg. 768): Carrasco discloses vitamin B12, the methylmalonic acid lowering agent.

consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorochobalamin	
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B12.	*See* Carrasco (pg. 768): As discussed above with respect to the "the methylmalonic acid lowering agent is selected from…" element of claim 1, Carrasco discloses that the methylmalonic acid lowering agent is vitamin B12.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* Carrasco (pg. 768): As discussed above with respect to the "and an effective amount of methylmalonic acid lowering agent" limitation of claim 1, Carrasco discloses parenteral administration of vitamin B12, which one skilled in the art would recognize as being an intramuscular injection. *See* Ex. 1011, Cole Declaration at ¶ 54. The amount and manner in which vitamin B12 is administered is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. In fact, the '209 Patent states as much: "it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in light of the relevant circumstances…" *See* Ex. 1001, '290 Patent, Col. 5, lines 37-50. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
4. The method of claim	As discussed above with respect to claim 3, one skilled

2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	in the art would have recognized parenteral administration of vitamin B12 as being an intramuscular injection, Ex. 1011, Cole Declaration, at ¶ 54, and have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
5. The method of claim 2, 3 or 4, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
6. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
7. The method of claim 5 wherein the folic acid is administered from about 1 to about 24 hours prior to	*See* Hammond (Abstract): Hammond discloses administering folic acid to patients at any time starting 2 days before administering pemetrexed disodium.

administration of the pemetrexed disodium.	
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.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium. A person skilled in the art would recognize oral administration as a common method of administering folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶ 54.
9. The method of claim 8 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
10. The method of claim 9 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to orally administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein, the improvement comprises:	*See* Hammond (Abstract): Hammond discloses administering pemetrexed disodium to cancer patients in phase I trials.
a) administration of between about 350 µg and about 1000 µg of	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium.

folic acid prior to the first administration of pemetrexed disodium;	Based on the teachings of Carrasco and Hammond, the amount of and timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration at ¶¶ 52-54, ¶ 62.
b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the timing of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration at ¶¶ 52-54, ¶ 62.
c) administration of pemetrexed disodium.	*See* Hammond (Abstract): Hammond discloses administering pemetrexed disodium.
14. The method of claim 12, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner and timing of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
15. The method of claim 14, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner and timing of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to

	administer about 1000 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
16. The method of claim 15, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium.
17. The method of claim 16 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
18. The method of claim 17 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Hammond (Abstract): Hammond discloses administering 5 mg of folic acid starting 2 days before administering pemetrexed disodium. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to orally administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.
19. The method of claim 18 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.	*See* Hammond (Abstract): Hammond discloses administering folic acid 5 mg to patients at any time starting 2 days before administering pemetrexed disodium. Based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.

20. The method of claim 18 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	*See* Hammond (Abstract): Hammond discloses administering folic acid 5 mg to patients at any time starting 2 days before administering pemetrexed disodium.
21. The method of claim 12, 18 or 19, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 62.

B. GROUND 2: CLAIMS 1-10, 12, AND 14-21 ARE OBVIOUS OVER CARRASCO AND CALVERT

Claims 1-10, 12, and 14-21 of the '209 patent are obvious over Carrasco and Calvert.

i. Scope and Content of Prior Art

a. Carrasco

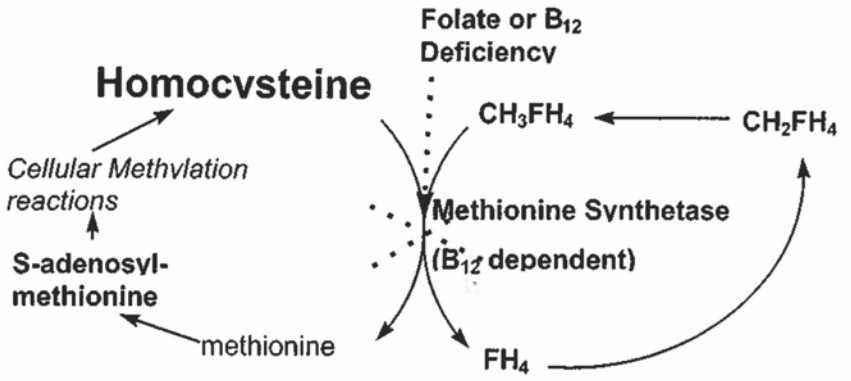
The discussion of Carrasco in Section (V)(A)(i) above is incorporated herein.

b. Calvert

Calvert discloses administering pemetrexed to patients and that pemetrexed toxicity is predicted by increases in homocysteine levels. Calvert teaches that

pemetrexed has a broad spectrum of preclinical activity and an encouraging level of activity, documented in early phase II clinical trials. Ex. 1005, Calvert at 9.

Calvert examines the toxicity resulting from treatment with antifolates, such as pemetrexed (MTA), and explains that "[t]he measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting toxicity of MTA [(pemetrexed)]." *Id*. Moreover, Calvert teaches that "any functional deficiency either in B12 or folate will result in reduction in flux through methionine synthase and a consequent increase in the plasma level of homocysteine." *Id*. at 8; Fig. 8, reproduced below; *see also* Ex. 1011 Cole Declaration, at ¶ 32.



Calvert also discloses that patients treated with antifolates, such as pemetrexed, who have also been administered folic acid, exhibit a maximum tolerated dose at least 10-fold higher than patients who do not receive folate supplementation. *See* Ex. 1005, Calvert at 7.

ii. Claims 1-10, 12 and 14-21 are Obvious in view of Carrasco and Calvert

A person of ordinary skill in the art would have been highly motivated to combine the teachings of Carrasco and Calvert to administer folic acid and vitamin B12 in conjunction with pemetrexed. Ex. 1011, Cole Declaration at ¶ 70. As discussed above for Ground 1, a person of ordinary skill in the art would have been motivated to reduce toxicity caused by pemetrexed disodium by combining Carrasco - which teaches that vitamin B12 can be administered along with folic acid in order to reduce the toxicity associated with an antifolate - with Calvert - which teaches that deficiencies in folate or vitamin B12 increase homocysteine levels and that treating patients with folic acid reduces pemetrexed toxicity. *See* Ex. 1011, Cole Declaration, at ¶ 70. In other words, administering vitamin B12 and folic acid along with pemetrexed is obvious at least because it is a predictable variation of art that teaches administration of vitamin B12 and folic acid along with methotrexate. *See KSR Int'l Co.*, 127 S. Ct. at 1740; *see also* Ex. 1011, Cole Declaration, at ¶ 70.

The tables below show how each limitation of claims 1-10, 12, and 14-21 is met by Carrasco and Calvert.

Claims of the '209 patent	**Carrasco and Calvert**
1. A method for administering pemetrexed disodium to a patient in need thereof comprising	*See* Calvert (pg. 9): Calvert discloses that pemetrexed "has a broad spectrum of preclinical activity…and has an encouraging level of activity documented in early phase II clinical trials."
administering an effective amount of folic acid	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Calvert also notes that "the effect of folic supplementation on reducing the toxicity of antifolate drugs (particularly the GARFT inhibitors) is clear." *See* Ex. 1005, Calvert at 8.
and an effective amount of methylmalonic acid lowering agent	*See* Carrasco (pg. 768): Carrasco discloses administering "parenteral vitamin B12 2 mg/day for 4 consecutive days" to ameliorate toxicity and reduce homocysteine levels. It would have been obvious to modify Calvert to addionally administer methylmalonic acid lowering agent to lower homocysteine levels. *See* Ex. 1011, Cole Declaration, at ¶ 70.
followed by administering an effective amount of pemetrexed disodium, wherein	*See* Calvert (pg. 9): Calvert discloses that pemetrexed "has a broad spectrum of preclinical activity…and has an encouraging level of activity documented in early phase II clainical trials." The order in which the vitamins are administered vis-à-vis the administration of pemeterxed is a matter of a physician's preference. *See* Ex. 11, Cole Declaration, at ¶¶ 52-54. As a result, one skilled in the art would have arrived at the order in which the vitamins are administered without undue experimentation. *Id*.
the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12,	*See* Carrasco (pg. 768): Carrasco discloses vitamin B12, the methylmalonic acid lowering agent.

hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorochobalamin	
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B12.	*See* Carrasco (pg. 768): As discussed above with respect to the "the methylmalonic acid lowering agent is selected from…" element of claim 1, Carrasco discloses that the methylmalonic acid lowering agent is vitamin B12.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* Carrasco (pg. 768): As discussed above with respect to the "and an effective amount of methylmalonic acid lowering agent" limitation, Carrasco discloses parenteral administration of vitamin B12, which one skilled in the art would recognize as being an intramuscular injection. *See* Ex. 1011, Cole Declaration, at ¶ 54. The amount and manner in which vitamin B12 is administered is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. In fact, the '209 Patent states as much: "it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in light of the relevant circumstances…" See Ex. 1001, '209 Patent Col. 5, lines 37-50. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation.
4. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000	As discussed above with respect to claim 3, one skilled in the art would have recognized parenteral administartion of vitamin B12 as being an intramuscular injection, Ex. 1011, Cole Dealaration, at ¶ 54, and have arrived at the specific dosage amounts for vitamin B12

µg.	and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
5. The method of claim 2, 3 or 4, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70#.
6. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Hammond, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
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.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, the timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of the

	pemetrexed disodium without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
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.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. A person skilled in the art would recognize oral administration as a common method of administering folic acid without undue experimentation. Ex. 1011, Cole Declaration at ¶ 54.
9. The method of claim 8 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
10. The method of claim 9 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to orally administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein, the improvement comprises:	*See* Calvert (pg. 9): Calvert discloses that pemetrexed "has a broad spectrum of preclinical activity…and has an encouraging level of activity documented in early phase II clainical trials."
a) administration of between about 350 µg and about 1000 µg of	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels.

folic acid prior to the first administration of pemetrexed disodium;	Based on the teachings of Carrasco and Calvert, the amount and timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
c) administration of pemetrexed disodium.	*See* Calvert (pg. 9): Calvert discloses that pemetrexed "has a broad spectrum of preclinical activity…and has an encouraging level of activity documented in early phase II clainical trials."
14. The method of claim 12, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
15. The method of claim 14, wherein the vitamin B12 is administered as an intramuscular	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation.

injection of about 1000 µg.	Accordingly, based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
16. The method of claim 15, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
17. The method of claim 16 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
18. The method of claim 17 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, one skilled in the art would have known to orally administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
19. The method of claim 18 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, the timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art

	would have known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
20. The method of claim 18 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	*See* Carrasco (pg. 768): Carrasco discloses administering "folic acid 5 mg/day…for 14 days" to ameliorate toxicity and reduce homocysteine levels. Based on the teachings of Carrasco and Calvert, the timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.
21. The method of claim 12, 18 or 19, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Carrasco and Calvert, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 70.

C. GROUND 3: CLAIMS 1-10, 12, AND 14-21 ARE OBVIOUS OVER NIYIKIZA AND EP005

Claims 1-10, 12, and 14-21 of the '209 patent are obvious over Niyikiza and EP005.

i. Scope and Content of the Prior Art

a. Niyikiza

Niyikiza discloses a statistical analysis that demonstrated the correlation between increased homocysteine (Hcys) levels and pemetrexed toxicity. Specificallyl, Niyikiza describes a study of 118 patients treated with pemetrexed during a phase II trial. Ex. 1006, Niyikiza at Abstract. 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 reports that

> [t]here was a strong correlation between baseline homocysteine levels and the development of the folowing toxicities at any time during the study: CTC Grade 4 neutropenia (57 pts, $p < 0.0001$), Grade 4 thrombocytopenia (13 pts, $p < 0.0001$), Grade 3 or 4 mucositis (8 pts, $p < 0.0003$), and Grade 3 or 4 dirrhea (8 pts, $p < 0.004$).

Id. Niyikiza further discloses that "[t]oxicity was seen in ***all*** patients with homocysteine levels above a threshold concentration of 10 [Mu]M. *Id*. (emphasis added).

Niyikiza is highly material to the validity of the claims of the ‘209 Patent. Niyikiza discloses a method of administering pemetrexed to a patient in need and that elevated levels of homocysteine correlate with pemetrexed toxicity. *Id.* In view of this disclosure, a person having ordinary skill in the art would have

employed known methods to lower homocysteine levels and reduce antifolate toxicity, such as the administration of an effective amount of folic acid and methylmalonic acid lowering agent. *See* Ex. 1011, Cole Declaration at ¶ 36.

b. European Patent Application Number 0595005

EP005 discloses administration of a pharmaceutical preparation of vitamin B6, folate and vitamin B12 for lowering levels of homocysteine caused by "***any known cause***, including…[d]rugs which induce elevated homocysteine levels including[ing]…***methotrexate….***" Ex. 1009, EP005 at 4 (emphasis added). EP005 further explains that deficiencies of vitamin B6, folate, and vitamin B12 are known to be associated with increased homocysteine levels. *Id*. at 3. Moreover, EP005 reports that a "synergism exists when vitamin B12, folate and vitamin B6 are given concurrently." *Id*. at 11.

EP005 also discloses how the claimed preparation of vitamin B6, folic acid and vitamin B12 is administered. In particular, administration of the preparation can occur after homocysteine levels become elevated to normalize levels, or prophylactically to prevent elevation of homocysteine. *Id*. at 4. Furthermore, the preparation may be formulated for oral administration or intramuscular injection. *Id*. at 5. EP005 also provides exemplary ranges for administration (μg/d/kg body weight):

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

(*Id*. at 5).

ii. Claims 1-10, 12 and 14-21 are Obvious in view of Niyikiza and EP005

In view of the known problem of antifolate toxicity, it would have been obvious to combine the teachings of Niyikiza and EP005. *See* Ex. 1011, Cole Declaration, at ¶¶ 77-78. In particular, a person having ordinary skill in the art would have been highly motivated to combine Niyikiza - which teaches that pemetrexed toxicity correlates with elevated levels of homocysteine - with EP005 - which teaches that pre-administration of vitamin B6, folic acid, and vitamin B12 in ranges that encompass those recited in the '209 patent claims lowers elevated levels of homocysteine caused by treatment with the antifolate methotrexate. Ex. 1011, Cole Declaration, at ¶ 77. Given that there are only a finite number of identified predictable solutions for lowering homocysteine levels, administering vitamin B12 and folic acid along with pemetrexed is obvious at least because it is a predictable variation of art that teaches administration of vitamin B12 and folic acid along with methotrexate. *See KSR Int'l Co.*, 127 S. Ct. at 1732; *see also* Ex. 1011, Cole Declaration, at ¶ 77.

While EP005 does not disclose the specific timing or duration of treatment recited in the '209 Patent claims, as discussed above, a physician routinely makes these types of determinations based on a patient's partiular circumstances. *See* Ex. 1001, '209 Patent, at Col. 5, lines 37-41, Ex. 1011, Cole Declaration, at ¶¶ 52-54. Accordingly, one of ordinary skill in the art would have arrived at the order, amount, duration, and manner of administering folic acid and vitamin B12 without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54.

The tables below show how each limitation of claims 1-10, 12 and 14-23 is met by Niyikiza and EP005.

Claims of the '209 patent	**Niyikiza and EP005**
1. A method for administering pemetrexed disodium to a patient in need thereof comprising	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials treated with pemetrexed.
administering an effective amount of folic acid	*See* EP005 (pg. 5): EP005 teaches administration of a pharmaceutical preparation of vitamin B6, ***folate*** and vitamin B12 that lowers "total homocysteine blood levels if elevated ***by any known cause***, including…[d]rugs which induce elevated homocysteine levels including[ing]…***methotrexate***...." (emphasis added) In view of EP005, it would have been obvious to modify Niyikiza to administer vitamin B12 along with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
and an effective amount of methylmalonic acid	*See* EP005 (pg. 5): EP005 teaches administration of a pharmaceutical preparation of vitamin B6, ***folate*** and

lowering agent	vitamin B12 that lowers "total homocysteine blood levels if elevated ***by any known cause***, including…[d]rugs which induce elevated homocysteine levels including[ing]…***methotrexate***...." (emphasis added) In view of EP005, it would have been obvious to modify Niyikiza to administer vitamin B12 along with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
followed by administering an effective amount of pemetrexed disodium, wherein	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials. The order in which the vitamins are administered vis-à-vis the administration of pemeterxed is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. As a result, one skilled in the art would have arrived at the order in which the vitamins are administered without undue experimentation.
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 chlorochobalamin	*See* EP005 (Abstract): EP005 discloses vitamin B12, the methylmalonic acid lowering agent.
2. The method of claim 1, wherein the methylmalonic acid lowering agent is	*See* EP005 (Abstract): As discussed above with respect to the "the methylmalonic acid lowering agent is selected from…" element of claim 1, EP005 discloses that the methylmalonic acid lowering agent is vitamin

vitamin B12.	B12.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* EP005 (pg. 5): EP005 discloses administration of vitamin B12 in a range of 1, 5-75 (µg/d/kg body weight), which overlaps a dosage of about 500 µg to about 1500 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. The amount and manner in which vitamin B12 is administered is a matter of a physician's preference. Ex. 11, Cole Declaration, at ¶¶ 52-54. In fact, the '209 Patent states that "it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in light of the relevant circumstances…" *See* Ex. 1001 ,col. 5, lines 37-50. Based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation.
4. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	*See* EP005 (pg. 5): EP005 discloses administration of vitamin B12 in a range of 1, 5-75 (µg/d/kg body weight), which overlaps a dosage of about 1000 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 77-78.
5. The method of claim 2, 3 or 4, wherein 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	*See* EP005 (pg. 5): EP005 discloses that the pharmaceutical preparation including folic acid, vitamin B6 and vitamin B12 may be administed prophylacticly to prevent elevated levels of homocysteine. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex.

pemetrexed disodium is discontinued.	1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 77-78.
6. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* EP005 (pg. 5): EP005 discloses that vitamin B12 is administered as an intramuscular injection in a range of 1,5-75 (µg/d/kg body weight), which overlaps a dosage of about 500 µg to about 1500 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. Ex. 1011, Cole Declaration, at 77-78.
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.	*See* EP005 (pg. 5): EP005 discloses that the pharmaceutical preparation including folic acid, vitamin B6 and vitamin B12 may be administed prophylacticly to prevent elevated levels of homocysteine. The timing of administration of folic acid is a matter of physician prefernece. Ex. 1011, Cole Declaration, at ¶¶ 52-54. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of the pemetrexed disodium without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
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.	*See* EP005 (pg. 5): EP005 discloses oral administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of between 0.3 mg to about 5 mg. Ex. 1011, Cole Declaration, at 48-49. A person skilled in the art would recognize oral administration as a common method of admnistering foilc acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶ 54.
9. The method of claim 8 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* EP005 (pg. 5): EP005 discloses administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of about 350 µg to about 1000 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Based on the teachings of Niyikiza and EP005, one

	skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
10. The method of claim 9 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* EP005 (pg. 5): EP005 discloses administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of between 350 µg to about 600 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about 350 µg to about 600 µg of folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein, the improvement comprises:	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials treated with pemetrexed.
a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium;	*See* EP005 (pg. 5): EP005 teaches prophylactic administration of a pharmaceutical preparation of vitamin B6, ***folate*** and vitamin B12 that lowers "total homocysteine blood levels if elevated ***by any known cause***, including . . . [d]rugs which induce elevated homocysteine levels including[ing]… ***methotrexate***…." (emphasis added) The amount and timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 52-54.
b) administration of about 500 µg to about	*See* EP005 (pg. 5): EP005 teaches prophylactic administration of a pharmaceutical preparation of

1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and	vitamin B6, ***folate*** and vitamin B12 that lowers "total homocysteine blood levels if elevated ***by any known cause***, including . . . [d]rugs which induce elevated homocysteine levels including[ing]… ***methotrexate***…." (emphasis added) Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
c) administration of pemetrexed disodium.	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials.
14. The method of claim 12, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* EP005 (pg. 5): EP005 discloses that vitamin B12 is administered as an intramuscular injection in a range of 1,5-75 (µg/d/kg body weight), which overlaps a dosage of about 500 µg to about 1500 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.
15. The method of claim 14, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	*See* EP005 (pg. 5): EP005 discloses that vitamin B12 is administered as an intramuscular injection in a range of 1,5-75 (µg/d/kg body weight), which overlaps a dosage of about 1000 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about about 1000 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 77-78.

16. The method of claim 15, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	*See* EP005 (pg. 5): EP005 discloses oral administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of 0.3 mg to about 5 mg. Ex. 1011, Cole Declaration, at ¶¶ 48-49. A person skilled in the art would recognize oral administration as a common method of administering folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶ 54.
17. The method of claim 16 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* EP005 (pg. 5): EP005 discloses oral administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of 350 µg to about 1000 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49.
18. The method of claim 17 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* EP005 (pg. 5; Fig. 8): EP005 discloses oral administration of folic acid in an amount of 1,5-150 (µg/d/kg body weight), which overlaps a dosage of 350 µg to about 600 µg. Ex. 1011, Cole Declaration, at ¶¶ 48-49.
19. The method of claim 18 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.	*See* EP005 (pg. 5): EP005 discloses that the pharmaceutical preparation including folic acid, vitamin B6 and vitamin B12 may be administed prophylacticly to prevent elevated levels of homocysteine. The timing of administration of folic acid is a matter of physician preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. Accordingly, one skilled in the art would have known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. Ex. 1011, Cole Declaration, at ¶ 78.

20. The method of claim 18 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	*See* EP005 (pg. 5): EP005 discloses that the pharmaceutical preparation including folic acid, vitamin B6 and vitamin B12 may be administed prophylacticly to prevent elevated levels of homocysteine. The timing of administration of folic acid is a matter of physician preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. Accordingly, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of pemetrexed disodium without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 78.
21. The method of claim 12, 18 or 19, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule and duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Niyikiza and EP005, one skilled in the art would have known to administer about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 78.

D. GROUND 4: CLAIMS 1-10, 12, AND 14-21 ARE OBVIOUS OVER NIYIKIZA AND REFSUM

Claims 1-10, 12, and 14-21 of the '209 patent are obvious over Niyikiza and Refsum.

i. Niyikiza

The discussion of Niyikiza from section (V)(C)(i) above is incoporated herein.

ii. Refsum

Refsum discloses the causes and clinical implications of elevated homocysteine levels. *See* Ex. 1008, Refsum, at Abstract. Refsum explains that even low doses of the antifolate methotrexate induce increased plasma homocysteine levels. *Id*. at 415. Furthermore, folic acid and vitamin B12 are both necessary for reduction of homocysteine levels. *Id*. at 412. In particular, Refsum teaches that

> the fate of intracellular homocysteine is either resalvage to methionine through remethylation, or conversion to cysteine via the trans-sulfuration pathway. In most tissues, the former reaction is catalyzed by the ubiquitous enzyme methionine synthase (Fig. 1). This enzyme requires vitamin B12 [methyl(I)cobalamin] as a cofactor and 5-methyl-tetrahydrofolate [(folic acid)] as methyl donor [cosubstrate]…

Id. at 411.

Refsum also explains that deficiencies in folic acid or vitamin B12 are common causes of elevated plasma homocysteine. "[T]here is a negative correlation between serum cobalamin and total plasma homocysteine…Similarly, folate deficiency is a common cause of elevated plasma homocysteine levels." *Id*. at 412. Consequently, Refsum teaches that administering compounds serving as co-factors in homocysteine metabolism, such as folic acid or vitamin B12, "may enhance homocysteine metabolism and thereby reduce plasma homocysteine levels…." *Id*. at 412-413.

iii. Claims 1-10, 12 and 14-21 of the '209 Patent are obvious in view of Niyikiza and Refsum

A person having ordinary skill in the art would have considered claims 1-10, 12 and 14-21 obvious in view of Niyikiza and Refsum. As discussed above in Grounds 1-3, toxicity resulting from treatment with antifolates was a well-known problem in the field of cancer therapeutics. *See* Ex. 1011, Cole Declaration, at ¶ 31. A person of ordinary skill in the art therefore would have been highly motivated to combine Niyikiza - which teaches that pemetrexed toxicity correlates with elevated levels of homocysteine with Refsum - which teaches that administering folic acid and vitamin B12 may reduce plasma homocysteine levels. Ex. 1011, Cole Declaration, at ¶ 83. Given that there are only a finite number of identified, predictable solutions for lowering homocysteine levels, it would have been obvious to one skilled in the art to administer vitamin B12 and folic acid along with pemetrexed. *See KSR Int'l Co.*, 127 S. Ct. at 1732; *see also* Ex. 1011, Cole Declaration, at ¶ 83.

While Refsum does not expressly disclose the order or amounts of folic acid and vitamin B12 administered in certain of the '209 claims, as discussed above, a physician routinely makes these types of determinations based on a patient's particular circumstances. *See* Ex. 1001,'209 Patent, at Col, 5, lines 37-50; *see also* Ex. 1011, Cole Declaration, at ¶¶ 52-54. . Accordingly, one of ordinary skill in the art would have arrived at the order, amount, duration, and manner of administering

folic acid and vitamin B12 without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 52-54.

Provided below are tables showing how each recitation of claims 1-11, 12 and 14-22 are met by Niyikiza and Refsum.

Claims of the '209 patent	**Niyikiza and Refsum**
1. A method for administering pemetrexed disodium to a patient in need thereof comprising	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials treated with pemetrexed.
administering an effective amount of folic acid	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." It would have been obvious to modify Niyikiza to administer vitamin B12 along with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶¶ 83-84.
and an effective amount of methylmalonic acid lowering agent	*See* Refsum (pg. 412): Refsum discloses that "[c]ompounds serving as co-factors in homocysteine catabolism or remethylation[, such as vitamin B12,] may enhance homocysteine metabolism and thereby reduce plasma homocysteine levels…." It would have been obvious to modify Niyikiza to administer vitamin B12 along with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶¶ 83-84.
followed by administering an effective amount of pemetrexed disodium, wherein	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials. The order in which the vitamins are administered vis-à-vis the administration of pemeterxed is a matter of a physician's preference. Ex. 1011, Cole Declaration, at

	¶¶ 52-54. As a result, one skilled in the art would have arrived at the order in which the vitamins are administered without undue experimentation.
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 chlorochobalamin	*See* Refsum (pg. 412): Refsum discloses vitamin B12, the methylmalonic acid lowering agent.
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B12.	*See* Refsum (pg. 412): As discussed above with respect to the "the methylmalonic acid lowering agent is selected from…" element of claim 1, Refsum discloses that the methylmalonic acid lowering agent is vitamin B12.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* Refsum (pg. 412): Refsum discloses that "[c]ompounds serving as co-factors in homocysteine catabolism or remethylation[, such as vitamin B12,] may enhance homocysteine metabolism and thereby reduce plasma homocysteine levels…." The amount and manner in which vitamin B12 is administered is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. In fact, the '209 Patent states that "it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in light of the relevant circumstances…" *See* Ex. 1001, '209 Patent, Col. 5, lines 37-50. Based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer 500

	µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation.
4. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
5. The method of claim 2, 3 or 4, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶52-54, ¶¶ 83-84.
6. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
7. The method of claim 5 wherein the folic acid is administered from about 1 to about 24	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." The timing of administrationof folic acid is a matter of

hours prior to administration of the pemetrexed disodium.	physician preference. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of the pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
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.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." A person skilled in the art would recognize oral administration as a common method of administering folic acid without undue experimentation. Ex. 1011, Cole Declaration at ¶ 54.
9. The method of claim 8 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." Based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at 52-54, ¶¶ 83-84.
10. The method of claim 9 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." Based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein, the improvement	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials treated with pemetrexed.

comprises:	
a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium;	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." The amount and timing of folic acid administration is a matter of physician preference. Accordingly, one skilled in the art would have known to orally administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
c) administration of pemetrexed disodium.	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials.
14. The method of claim 12, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
15. The method of claim 14, wherein the vitamin B12 is administered as	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of

an intramuscular injection of about 1000 µg.	administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about about 1000 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
16. The method of claim 15, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." A person skilled in the art would recognize oral administration as a common method of administering folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶ 54.
17. The method of claim 16 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." Based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
18. The method of claim 17 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
19. The method of claim 18 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." The timing of administration of folic acid is a matter of physician preference. Ex. 1011, Cole Declaration at ¶¶ 52-54. Accordingly, one skilled in the art would have

	known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
20. The method of claim 18 wherein the folic acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	*See* Refsum (pg. 413): Refsum teaches that "[f]olic acid (5 mg daily) efficiently decreases plasma homocysteine levels." The timing of administration of folic acid is a matter of physician preference. Ex. 1011, Cole Declaration at ¶¶ 52-54. Accordingly, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.
21. The method of claim 12, 18 or 19, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Niyikiza and Refsum, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶¶ 83-84.

E. GROUND 5: CLAIMS 1-10, 12, AND 14-21 ARE OBVIOUS OVER NIYIKIZA AND MALINOW

Claims 1-10, 12, and 14-21 of the '209 patent are obvious over Niyikiza and Malinow.

i. Scope and Content of Prior Art

a. Niyikiza

The discussion of Niyikiza from Section (V)(C)(i) above is incorporated herein.

b. Malinow

Malinow examines the homocysteine lowering effects caused by administering folic acid and multivitamins that contain vitamin B12. *See* Ex. 1007, Malinow, at Abstract. Malinow reports that both folic acid (FA) and multivitamins that contain vitamin B12 reduce concentration of plasma total homocysteine. *Id*. at 5. "Our findings demonstrated a significant negative correlation between tHcy and basal levels of folate, P5'P, and B12; the simultaneous intake of these vitamins in multivitamins may be involved in interactions that could partially account for these associations. *Id*. Furthermore, "[i]t could be broadly surmised that individuals in whom tHcy levels are not lowered by FA supplementation . . . additional treatment with other agents, such as pyridoxine, cobalamin [(vitamin B12)], or betaine, may be advisable. *Id*. at 5-6.

ii. Claims 1-10, 12 and 14-21 are Obvious over Niyikiza and Malinow

It would have been obvious to combine the teachings of Niyikiza and Malinow. As discussed above in Ground 1, it is apparent that the industry was continually attempting to reduce toxicity associated with antifolates, such as

pemetrexed, by *inter alia* reducing homocysteine levels. *See* Ex. 1011, Cole Declaration, at ¶ 31. A person having ordinary skill in the art therefore would have been highly motivated to combine Niyikiza - which teaches that pemetrexed toxicity correlates with elevated homocysteine levels - with Malinow - which teaches that administering folic acid and vitamin B12 reduces plasma homocysteine levels. *See* Ex. 1011, Cole Declaration, at ¶ 88. Given that there are only a finite number of identified, predictable solutions for lowering homocysteine levels, it would have been obvious to one skilled in the art to administer vitamin B12 and folic acid. *See KSR Int'l Co.*, 127 S. Ct. at 1732; *see also* Ex. 1011, Cole Declaration, at ¶ 88.

Malinow does not expressly disclose the order or exact amounts of folic acid and vitamin B12 administered in the '209 Patent claims; however, as discussed above, the '209 Patent provides that a physician determines the administration protocol, considering various factors. *See* Ex. 1001, '209 Patent, at Col, 5, lines 37-50. This indicates that one of ordinary skill in the art would have arrived at the order, amount, duration, and manner of administering folic acid and vitamin B12 without undue experimentation. Ex. 1011, Cole Declaration, at ¶ 89.

The tables below show how each limitation of claims 1-10, 12 and 14-23 is met by Niyikiza and Malinow.

Claims of the '209 patent	**Niyikiza and Malinow**
1. A method for administering pemetrexed disodium to a patient in need thereof comprising	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials who were treated with pemetrexed.
administering an effective amount of folic acid	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. It would have been obvious to modify Niyikiza to administer vitamin B12 aong with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶ 88.
and an effective amount of methylmalonic acid lowering agent	*See* Malinow (pg. 5): Malinow discloses that patients taking a multivitamin containing vitamin B12 exhibited a "significant negative correlation" between levels of homocysteine and vitamin B12. It would have been obvious to modify Niyikiza to administer vitamin B12 aong with folic acid to lower homocysteine levels. Ex. 1011, Cole Declaration, at ¶ 88.
followed by administering an effective amount of pemetrexed disodium, wherein	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials. The order in which the vitamins are administered vis-à-vis the administration of pemeterxed is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. As a result, one skilled in the art would have arrived at the order in which the vitamins are administered without undue experimentation.
the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin,	*See* Malinow (pg. 5): Malinow discloses vitamin B12, the methylmalonic acid lowering agent.

cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorochobalamin	
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B12.	*See* Malinow (pg. 5): As discussed above with respect to the "the methylmalonic acid lowering agent is selected from…" element of claim 1, Malinow discloses that the methylmalonic acid lowering agent is vitamin B12.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*See* Malinow (pg. 5): Malinow discloses that patients taking a multivitamin that contained vitamin B12 exhibited a "significant negative correlation" between levels of homocysteine and vitamin B12. The amount and manner in which vitamin B12 is administered is a matter of a physician's preference. Ex. 11, Cole Declaration, at ¶¶ 52-54. In fact, the '209 Patent states that "it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in light of the relevant circumstances…" Ex. 1001, '209 Patent, Col. 5, lines 37-50. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation.
4. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 1000 µg of vitamin B12 as an

	intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
5. The method of claim 2, 3 or 4, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage schedule or duration for vitamin B12 without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer vitamin B12 about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
6. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at 52-54, ¶ 89.
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.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. The timing of administration of folic acid is a matter of a physician's preference. Ex. 1011, Cole Declaration, at ¶¶ 52-54. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of the pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
8. The method according to any one of	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three

claims 1-4, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	weeks decreases homocysteine levels. A person skilled in the art would recognize oral administration as a common method of administering folic Accordingly, one skilled in the art would have known to orally administer about 0.3 mg to about 5 mg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
9. The method of claim 8 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
10. The method of claim 9 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein, the improvement comprises:	*See* Niyikiza (Abstract): Niyikiza discloses a study of 246 patients in phase II medical trials treated with pemetrexed.
a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza the amount and timing of folic acid administration is a matter of

pemetrexed disodium;	physician preference. Accordingly, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
c) administration of pemetrexed disodium.	*See* Niyikiza (Abstract): Niyikiza discloses administering pemetrexed to patients in phase II medical trials.
14. The method of claim 12, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 500 µg to about 1500 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
15. The method of claim 14, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about about 1000 µg of vitamin B12 as an intramuscular injection prior to the first administration of pemetrexed without undue experimentation. *See* Ex.

	1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
16. The method of claim 15, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. A person skilled in the art would recognize oral administration as a common method of administering folic Accordingly, one skilled in the art would have known to orally administer about 0.3 mg to about 5 mg of folic acid without undue experimentation. Ex. 1011, Cole Declaration, at ¶¶ 52-54.
17. The method of claim 16 wherein between 350 µg to about 1000 µg of folic acid is administered.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 350 µg to about 1000 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
18. The method of claim 17 wherein between 350 µg to about 600 µg of folic acid is administered.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about 350 µg to about 600 µg of folic acid without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
19. The method of claim 18 wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer folic acid 1 to 3 weeks prior to the first administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
20. The method of claim 18 wherein the folic	*See* Malinow (pg. 5): Malinow discloses that treating patients with 1 or 2 mg of folic acid every day for three

acid is administered from about 1 to about 24 hours prior to administration of the pemetrexed disodium.	weeks decreases homocysteine levels. Based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer folic acid from about 1 to about 24 hours prior to administration of pemetrexed disodium without undue experimentation. *See* Ex. 1011, Cole Declaration, at ¶¶ 52-54, ¶ 89.
21. The method of claim 12, 18 or 19, wherein 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.	As discussed above with respect to claim 3, one skilled in the art would have arrived at the specific dosage amounts for vitamin B12 and the manner of administering it without undue experimentation. Accordingly, based on the teachings of Niyikiza and Malinow, one skilled in the art would have known to administer about every 6 to about every 12 weeks following the administration ov vitamin B12 until the administration of the pemetrexed disodium is discontinued without undue experimentation. See Ex. 1011, Cole Declaration, at ¶¶ 52-54, 89.

F. GROUND 6: CLAIMS 11, 13, AND 22 ARE OBVIOUS OVER CARRASCO AND CALVERT AND THODTMANN

Claims 11, 13 and 22 of the '209 patent are obvious over Carrasco, Calvert and Thodtmann.

i. Scope and Content of Prior Art

a. Carrasco and Calvert

As discussed above in Ground 2, Carrasco and Calvert teach every limitation of claims 11, 13 and 22, except for co-administration of cisplatin. However, combination treatment therapy using an anti-cancer drug and cisplatin was well-

known in 1999, before the effective filing date of the application that matured into the '209 Patent. *See* Ex. 1011, Cole Declaration, at ¶¶ 55-57.

b. Thodtmann

Thodtmann, discloses co-administration of pemetrexed and cisplatin, evidencing this common knowledge. In Thodtmann, cander patients were treated with a combination of pemetrexed and cisplatin of varying concentrations to determine the maximum tolerated dose, dose limiting toxicities and pharmacokinetics of pemetrexed combined with cisplatin. *See* Thodtmann, Abstract. From this study, Thodtmann reports that "MTA [pemetrexed] may be safely combined with cisplatin and that this schedule is clinically active. We recommend MTA 500 mg/m2 plus cisplatin 75 mg/m2 as the dose to be used in phase II studies." Ex. 1010, Thodtmann, at 3016.

ii. Claims 11, 13 and 22 are obvious over Carrasco, Calvert and Thodtmann

In view of the foregoing, one skilled in the art would have recognized the advantages of administering pemetrexed disodium with cisplatin. As discussed above in Ground 2, Calvert and Carrasco teach administering folic acid and vitamin B12 in conjunction with administering pemetrexed to a patient in need thereof. Thodtmann further teaches that co-administering pemetrexed and cisplatin is safe and clinically active. Accordingly, it would have been obvious to one of

ordinary skill in the art to combine these known methods for obtaining predictable antineoplastic efficacy from combination therapy using cisplatin. *See KSR Int'l Co.*, 127 S. Ct. at 1731; *see also* Ex. 1011, Cole Declaration, at ¶ 92.

Although the Calvert, Carrasco and Thodtmann do not disclose the particular order and amounts of folic acid and vitamin B12 administered as recited in the claims; as discussed above in Ground 1, one of ordinary skill in the art would have arrived at the order, amount, duration, and manner of administering folic acid and vitamin B12 without undue experimentation. *See* Ex. 1001 ,'209 Patent, Col, 5, lines 37-50; Ex. 1011, Cole Declaration, at ¶¶ 92-93.

The tables below show how each limitation of claims 11, 13 and 22 is met by Carrasco, Calvert and Thodtmann.

Claims of the '209 patent	**Carrasco, Calvert and Thodtmann**
11. The method of claim 1 further comprising the administration of cisplatin to the patient.	*See* Thodtmann (pg. 3016): Thodtmann discloses that "MTA [pemetrexed] may be safely combined with cisplatin and that this schedule is clinically active." Accordingly, based on the teachings of Carrasco, Calvert and Thodtmann, one skilled in the art would have known to administer cisplatin in combination with pemetrexed. *See* Ex. 1011, Cole Declaration, at ¶¶ 92-93.
13. The method of claim 12 further comprising the administration of cisplatin to the patient.	*See* Thodtmann (pg. 3016): Thodtmann discloses that "MTA [pemetrexed] may be safely combined with cisplatin and that this schedule is clinically active." Based on the teachings of Carrasco, Calvert and Thodtmann, one skilled in the art would have known to

	administer cisplatin in combination with pemetrexed. *See* Ex. 1011, Cole Declaration, at ¶¶ 92-93.
22. The method of claim 21 further comprising the administration of cisplatin to the patient	*See* Thodtmann (pg. 3016): Thodtmann discloses that "MTA [pemetrexed] may be safely combined with cisplatin and that this schedule is clinically active." Accordingly, based on the teachings of Carrasco, Calvert and Thodtmann, one skilled in the art would have known to administer cisplatin in combination with pemetrexed. *See* Ex. 1011, Cole Declaration, at ¶¶ 92-93.

VII. CONCLUSION

Petitioner submits that issues have been presented that demonstrate a reasonable likelihood that claims 1-22 of the '209 Patent are unpatentable as obvious in view of the prior art. Petitioner therefore requests that the Board grant *inter partes* review for each of those claims.

Respectfully submitted,

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Dated: June 14, 2013

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Accord Healthcare, Inc.'s Petition for Inter Partes Review of U.S. Patent No. 7,772,209 and Exhibits 1000 – 1012 were served on June 14, 2013 via U.S. Mail to the correspondence address for the attorney of record for Eli Lilly and Company, the assignee of the '209 patent.

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