UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY, Plaintiff, v. TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS, LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA INC., BARR LABORATORIES, INC., Defendants.	)	Case No. 1:10-cv-01376-TWP-DKL

FINDINGS OF FACT AND CONCLUSIONS OF LAW FOLLOWING BENCH TRIAL AUGUST 19, 2013

This matter is before the Court for decision on the validity of claims 9, 10, 12, 14, 15, 18, 19 and 21 (the "Asserted Claims") of the U.S. Patent No. 7,772,209 (the "'209 Patent"). The '209 Patent is a method-of-use-patent which covers the co-administration of pemetrexed disodium ("pemetrexed") with two nutrients—folic acid and vitamin B12—that protect against the side effects of the drug ALIMTA®. The matter was before the Court for a bench trial beginning on August 19, 2013 and concluding on August 29, 2013. This is a Hatch-Waxman patent infringement action brought by Eli Lilly and Company ("Lilly"), the owner of the '209 Patent, against Defendants Teva Parenteral Medicines, Inc. ("Teva Parenteral"), Teva Pharmaceuticals USA, Inc. ("Teva Pharmaceuticals") (collectively with Teva Parenteral, "Teva"), APP Pharmaceuticals, LLC ("APP"), Barr Laboratories, Inc. ("Barr"), and Pliva Hrvatska d.o.o. ("Pliva") (collectively, "Defendants") arising out of Defendants' filing of Abbreviated New Drug Applications ("ANDAs") with the Food and Drug Administration ("FDA") seeking approval to market the pemetrexed disodium products identified in Teva's

ANDAs Nos. 90-352 and 90-674, APP's ANDA No. 90-384, and Barr's and Pliva's ANDA No. 91-111 (collectively the "ANDA Products") and covered under the '209 Patent.

As mentioned earlier, the '209 patent describes a method of administering a chemotherapy drug, pemetrexed, with vitamins, which is marketed by Lilly under the trade name ALIMTA®. Lilly is only asserting infringement of the Asserted Claims of the '209 Patent with respect to the ANDA Products. Each Defendant stipulates that under the Court's claim construction (Dkt. 115) and under the current laws of infringement, the sale of its ANDA Products, in accordance with the proposed labeling for each of those respective ANDA Products, would infringe the Asserted Claims of the '209 Patent, to the extent those claims are found valid and enforceable. Having heard testimony and considered the exhibits and arguments of the parties, the Court finds the Defendants have failed to show by clear and convincing evidence that the Asserted Claims of the '209 Patent are invalid for obviousness, obviousness-type double patenting, inadequate description or lack of enablement, and the Asserted Claims of the '209 Patent are valid and enforceable. In support thereof, the Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. FINDINGS OF FACT

A. The Parties

Plaintiff Lilly is a corporation organized and existing under the laws of the State of Indiana, having its corporate offices and principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285. Lilly is engaged in the business of research, development, manufacture and sale of pharmaceutical products throughout the world. Lilly sells pemetrexed in the United States under the trademark ALIMTA® for treatment of specific types of lung cancer and mesothelioma. ALIMTA® is covered under U.S. Patent No. 5,344,932, which is owned by The Trustees of Princeton University and licensed exclusively to Lilly.

The Defendants are all corporations primarily engaged in the business of making and selling drugs in generic form. Defendant Teva Parenteral is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 19 Hughes, Irvine, California 92618. Defendant Teva Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. Defendant APP is now Fresenius Kabi USA, LLC, a Delaware limited liability company with its principal place of business at Three Corporate Drive, Lake Zurich, Illinois 60047. Defendant Barr is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. Defendant Pliva is a limited liability company organized and existing under the laws of the Republic of Croatia with its principal place of business at Prilaz baruna Filipovica 25, 10000 Zagreb, Croatia.

B. The Patent-In-Suit

The patent-in-suit U.S. Patent No. 7,772,209, was issued to Lilly on August 10, 2010, and Lilly is the current owner of the '209 Patent. The '209 Patent covers the method of administration of ALIMTA®, requiring that physicians co-administer the drug with folic acid and vitamin B_{12} to reduce the incidence of patient toxicity caused by ALIMTA®.

C. History of Lilly's Antifolate Development Prior to the '209 Patent

1. Background on Antifolates

The '209 Patent describes a method of using an antifolate, pemetrexed, with vitamins. Antifolates are a type of chemotherapy drug used to treat certain types of cancer. Antifolates work by competing with folates, a class of essential nutrients that includes folic acid. Folates participate in chemical reactions in the body that make chemical precursors to DNA. DNA, in turn, is required for division and growth of both normal cells and cancer cells. Antifolates work

by interfering with the action of folates and deprive cancer cells of the DNA precursors they need to proliferate, or grow. Antifolates are used for their antiproliferative effect in the treatment of cancer to inhibit cell growth and division, which causes cancer cells to die. Because of the competitive relationship between folates and antifolates, the ability of an antifolate to fight cancer depends on the relative amount of folate and antifolate in the cell. As folate levels are increased, greater amounts of antifolates are needed to achieve an antiproliferative effect.

Cancer cells are fast-growing and thus have a high demand for DNA precursors, making them particularly susceptible to the effects of antifolates. However, fast growing normal cells, such as cells that line the gastrointestinal tract and cells of the bone marrow, also divide rapidly and are therefore also particularly susceptible to antifolates. Accordingly, the same mechanisms by which antifolates kill cancer cells also kill fast-growing normal cells, causing antifolate-related side effects referred to as "toxicities." Some of these toxicities – such as mucositis, anemia and low white blood cell counts– can be severe and even life-threatening.

Antifolate research began in 1948 with observations by Dr. Sidney Farber ("Dr. Farber") of children with leukemia. The children were given folic acid contained in liver extract, which Dr. Farber observed caused their tumor growth to accelerate. Based on that finding, Dr. Farber administered an experimental antifolate called aminopterin, which caused some of his patients to go into remission. Between 1950 and 1999, a great number of antifolates were made and tested, but as of 1999 the only antifolate approved by the FDA for treating cancer was methotrexate, which was approved in the 1950s. Methotrexate is also used in the treatment of rheumatoid arthritis ("RA"). Both cancer and RA patients experience toxicity from antifolates due to their antiproliferative effects – *i.e.* by killing rapidly dividing cells. However, unlike in cancer treatment, this antiproliferative effect is not the mechanism by which methotrexate treats RA.

2. Lilly's antifolate research and development in the 1990s

In the 1990s, Lilly had multiple antifolates in clinical use or development, including pemetrexed, lometrexol, and LY309887 (the "'887 compound"). In a few instances, researchers attempted to use folic acid pretreatment with antifolates in order to reduce the toxicities of the drug. Initial clinical trials of lometrexol, without any supplementation, were considered a "complete disaster" resulting in "appalling toxicities." Calvert Dep. Tr. 92:8-14. In an effort to address these severe toxicities, researchers tried administering lometrexol with folic acid. A Phase I clinical trial was conducted by Laohavinij[1] in 1996, which involved administering a daily oral dose of 5 mg of folic acid seven days before and seven days after lometrexol administration. TX 1036. However, the Laohavinij study of lometrexol with folic acid pretreatment reported only one response among folic acid supplemented patients, which was fewer than had been observed in earlier unsupplemented patients. TX 1036 at 333. Lilly had also pursued clinical development of a related antifolate, the '887 compound, which was also tested with folic acid pretreatment for the same reason as lometrexol, but as with lometrexol, those studies that attempted to reduce toxicity with folic acid supplementation proved unsuccessful due in part to the decrease in efficacy. In 1994, Lilly obtained U.S. Patent No. 5,217,974 (the "'974 Patent"). The '974 Patent claimed the use of folic acid pretreatment with a class of antifolates, with the preferred antifolate being lometrexol. TX 916.

One of the antifolate drugs Lilly had in development during the 1990s was pemetrexed. By the late 1990s, pemetrexed was viewed as a very promising anticancer drug. In April 1999, it was reported that phase II studies showed responses in six different tumor types, and the activity of the drug was considered "remarkable and unusual in a new drug of any class at this stage of

[1] Laohavinij, et al., *A Phase I clinical study of the antipurine antifolate lometrexol (DDATHF) given with oral folic acid*, INVESTIGATIONAL NEW DRUGS, 14: 325-335 (1996) (TX1036).

development." TX 907 at 107. In addition, as of June 1999, the toxicities associated with pemetrexed were considered "manageable and predictable" through dose and schedule adjustments, allowing for a broad scale of clinical use. *Id.*

D. Development of the '209 Patent

Dr. Clet Niyikiza ("Dr. Niyikiza") is a mathematician that was employed by Lilly in the 1990s to help with the clinical development of cancer compounds. In early 1997, Dr. Niyikiza performed a series of statistical analyses, known as multivariate analyses, on more than 60 variables in patients participating in pemetrexed clinical trials in efforts to better understand which patients were likely to develop the sporadic toxicities observed with pemetrexed. Dr. Niyikiza published the results of his multivariate analyses in two abstracts in 1998. TX 910 at 2139; TX 911 at 609P. The results of the analyses pointed to a correlation between the incidence of pemetrexed toxicities and patients' levels of homocysteine. Dr. Niyikiza reported that homocysteine levels of at least 10 micromolar correlated with specific pemetrexed toxicities. This amount is below the threshold for finding that a person has clinically high homocysteine levels, which is >15 micromolars. TX 1503 at 84; Green Tr. 540:9 –541:13. Thus, the homocysteine levels identified by Dr. Niyikiza as a marker for pemetrexed toxicity was a subclinical elevation level. Niyikiza Tr. 732:1-13.

Elevated homocysteine levels can be a marker for either folic acid or vitamin B_{12} deficiencies, among other conditions. Another substance, methylmalonic acid ("MMA"), is a predictor of vitamin B_{12} deficiency, but not folate deficiency. Thus, elevated homocysteine levels (without information about a patient's MMA levels) can indicate either folate deficiency or vitamin B_{12} deficiency, while elevated homocysteine *and* elevated MMA levels together indicate that the patient at least has a vitamin B_{12} deficiency. Importantly, elevated homocysteine *without* elevated MMA levels indicates that the patient does not have a vitamin

B_{12} deficiency. Analyzing data from a small set of patients receiving pemetrexed, Dr. Niyikiza found in his initial analyses, and published in his abstracts (TX 910, 911), that there was no statistical correlation between toxicity and the other variable he measured, including MMA, suggesting at the time that there was no correlation between toxicity and patients' vitamin B_{12} levels. Despite what he found in his initial analyses, Dr. Niyikiza still believed there was a connection between toxicity and patients' B_{12} levels. He suggested to Lilly, internally, that pretreating patients with a combination of low doses of vitamin B_{12} and folic acid would help reduce the frequency of sporadic toxicities observed by Lilly in its pemetrexed clinical trials. This idea was widely rejected by oncology experts both inside and outside Lilly, as the toxicities associated with pemetrexed were not viewed as problematic and they were concerned instead, that vitamin supplementation could adversely affect pemetrexed's efficacy. Calvert Dep. 124:7-125:25.

In late 1999, after the relevant priority date for this litigation, clinicians in the ongoing phase III pemetrexed registration trial in mesothelioma patients witnessed an alarming increase in drug-related patient deaths, around 7%; a 2% death rate was high enough to cause serious concerns with a drug in clinical trials. Niyikiza Tr. 795:16-26. Up until that point, pemetrexed's toxicity generally appeared to be manageable and tolerable; however, the sudden increase in patient deaths threatened to halt the development of the drug. Dr. Niyikiza reran his multivariate analysis on a larger database of patients, which this time revealed a "very strong" correlation between toxicities and elevated homocysteine, and additionally a stronger collinear nature between homocysteine and MMA, with about 15% of patients having very high levels of MMA. Niyikiza Tr. 796:17-797:2. This information was not previously known or disclosed at the time the Niyikiza abstracts were published. Niyikiza Tr. 797:3-7. Relying on the information about the increase in drug-related deaths, as well as further analyses of additional data by Dr. Niyikiza,

Lilly decided to implement Dr. Niyikiza's invention in the ongoing phase III registration trial by intervening with low levels of folic acid and vitamin B_{12} supplementation prior to administering pemetrexed. In a letter dated December 3, 1999, Lilly informed the FDA that the study protocol would be changed so that each patient in the study would receive 350 to 1000 µg of folic acid, with 500 µg being the recommended dose, and 1000 µg of vitamin B_{12} as an intramuscular injection. TX 330 at 3. The FDA response in January 2000 was that it did not support the addition of vitamins to the ongoing pemetrexed mesothelioma trial. TX 2100.

Despite the FDA's reservations, Lilly went ahead and implemented Dr. Niyikiza's vitamin supplementation regimen in the phase III mesothelioma trial. The result was that supplementing patients with low doses of folic acid and vitamin B_{12} prior to and during therapy mitigated pemetrexed's toxicities without hurting its efficacy. Dr. Niyikiza published his findings, including further analyses of the roles that folic acid and vitamin B_{12} each played in the observed toxicities, in 2002 in the "Molecular Cancer Therapeutics Journal." TX 80. Later in 2002, the results of the phase III trial of pemetrexed for mesothelioma, including data demonstrating that Dr. Niyikiza's vitamin supplementation regimen increased the rate of patients' response to pemetrexed therapy, were presented at the plenary session of the meeting of the American Society of Clinical Oncology. Niyikiza Tr. 845:4-17. The priority date for Lilly's patent application on Dr. Niyikiza's invention is June 30, 2000, and the '209 Patent was issued on August 10, 2010. Dr. Niyikiza is listed as the sole inventor of the '209 Patent.

E. Claims Asserted in the '209 Patent

Lilly is asserting claims 9, 10, 12, 15, 18, 19, and 21 of the '209 Patent with respect to the ANDA Products. TX 1 at cols. 11-12. Each claim requires pretreatment with a specified amount of folic acid, up to 1000 µg, and with vitamin B_{12} in the amount of 55-1,500 µg in claims 12, 14 and 21, and 1000 µg in claims 15, 18, and 19, prior to administering pemetrexed. Claims 19, 21,

and 22 further require a specific schedule for those pretreatments, and claims 15, 18 and 19 require administration of vitamin B_{12} by intramuscular injection.

F. Person of Ordinary Skill in the Arts

The Court previously determined, and the parties no longer dispute, that a person of ordinary skill in the art ("POSA") can be a medical doctor who specializes in oncology or a medical doctor with extensive experience in the areas of nutritional sciences involving vitamin deficiencies. However, as to the latter person, this individual would need to have collaborated with medical oncologists who have knowledge and experience in the treatment of cancer through the use of antifolates. *See* Dkt. 115 at 8.

II. CONCLUSIONS OF LAW

The '209 Patent is presumed to be valid under 35 U.S.C. § 282. *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984). Defendants, as the parties challenging the validity of the '209 Patent, bear the burden of proving invalidity by clear and convincing evidence. *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1282 (Fed. Cir. 2003). The Supreme Court has defined "clear and convincing" evidence as that which gives the finder of fact "an abiding conviction that the truth of [the proponent's] factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316 (1983).

A. The Asserted Claims in the '209 Patent are not Obvious

Defendants argue that each of the Asserted Claims in the '209 Patent are obvious. To prove obviousness, Defendants must show by clear and convincing evidence that "the differences between the subject matter [of the claims] and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). Obviousness is ultimately a legal conclusion

based on underlying factual findings, including (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (2) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness such as commercial success and satisfaction of a long-felt need. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

Thus, the Court must determine whether a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Id.* However, proving obviousness "requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements . . . ." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Under this legal standard for showing obviousness, Defendants must prove that a POSA would have had reason to (1) administer folic acid pretreatment with pemetrexed, (2) administer vitamin B_{12} pretreatment with pemetrexed, and (3) administer each of them according to the doses and schedules set forth in the Asserted Claims. Based upon the factual findings, the Court concludes that Defendants have not shown by clear and convincing evidence that a POSA would have been so motivated

1. Folic Acid Pretreatment with Pemetrexed was not Obvious

a. Worzalla & Hammond prior art

Defendants argue that Worzalla[2] (TX 384) or Hammond[3] (TX 911, 912) would have motivated a POSA to add folic acid pretreatment to pemetrexed in order to reduce toxicity.

[2] Worzalla, *et al.*, *Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY23154,* ANTI CANCER RESEARCH, 18:32353240 (1998) (TX384).

[3] Hammond, et at., *A phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514)* with folic acid (FA0, ANNALS OF ONCOLOGY, 9:129, Abstract 620P (1998)(TX911).

Worzalla, published in 1998, reports the results of a preclinical mouse study of folic acid pretreatment with pemetrexed. In the Worzalla study, folic acid was used in modulating the toxicity of pemetrexed in mice in three study groups: mice on a low-folate diet, mice that were given a low-folate diet along with folic acid supplementation, and a group of mice on a regular diet. The results of the study showed that for the mice on the low-folate diet that were supplemented with folic acid, anti-tumor activity was only maintained at much higher doses of the drug and at levels that would not have been tolerable to humans in clinical trials, or, as Lilly's expert Dr. Bruce A. Chabner ("Dr. Chabner") explained at trial, "astronomical doses" of pemetrexed were required to achieve antitumor efficacy in mice receiving folic acid supplementation as compared to unsupplemented mice. Chabner Tr. 1086:3-10; TX 884 at Tbl. 1; Zeisel Tr. 1598:17-22 (stating that mice supplemented with folic acid required 100 times the dose to obtain the same lethality of the cancer cells as unsupplemented mice); Green Tr. 524:11-16 (same). Despite the fact that Worzalla did not make a comparison between the standard diet group of mice and the supplemented and unsupplemented low-folate diet mice, the Defendants' expert, Dr. Mark J. Ratain ("Dr. Ratain"), testified that a POSA would compare the toxicity and efficacy observed in the standard diet and low-folate-plus-supplementation group of mice, and would recognize that based on the data from all three mouse groups that folate supplementation improved pemetrexed's therapeutic index. Ratain Tr. 164:23–165:7. Moreover, this was a comparison that Dr. Ratain made himself; the Worzalla paper contained no specific data on the dose response curve for the standard diet mice. Chabner Tr. 1252:14-1253:12.

Dr. Ratain's analysis does not take into account that a standard mouse diet contains a high amount of folate relative to what is required by humans. Zeisel Tr. 1595:23 – 1596:2. Dr. Ratain's analysis also does not account for the fact that the mice on the low-folate diets were also given an antibiotic, succinylsulfathiazole, to prevent bacteria in the mouse's intestine from

making folic acid even though it is not in the diet, while the standard diet mice were not. Zeisel Tr. 1596:2 – 1596:11. The lack of antibiotic in the standard diet mice permitted these mice to ingest higher levels of folate than what was contained in their food, as the mice would consume their waste product which contained folic acid produced in their intestines. Zeisel Tr. 1596:2-11; Green Tr. 385:9-20. As Lilly's expert Dr. Steven H. Zeisel ("Dr. Zeisel") stated, it would not be proper to compare the low-folate diet mice with the standard diet mice because there was a change in two variables in the study, not just one, and would be like "comparing an apple to an orange; it just isn't allowed in science." Zeisel Tr. 1596:23 – 1597:3.

A POSA would have recognized that there is difficulty in translating the results of a pre-clinical mouse study to results that would be seen in a human clinical trial, and additionally would not have concluded from the data in Worzalla that folic acid did not have an adverse impact on efficacy. As stated by Worzalla, mouse models have "poor predictive value . . . for antifolates toxicity." TX 384 at 3237; Chabner Tr. 1251:24–1252:3. It is possible to make qualitative conclusions from a mouse model and apply them to humans, but not quantitative conclusions. Chabner Tr. 1251:4-14. This is due in part to the fact that standard laboratory mice diets contain high levels of folic acid, thus the folate levels of mice on a low-folate diet fall to levels considered normal in humans. TX 384 at 3237. In addition, the tumor line used in the Worzalla mouse study was designed to be particularly sensitive to antifolates. Chabner Tr. 1334:10-17. However, even if a POSA did attempt to predict the results of folic acid supplementation in humans based upon the results in the Worzalla study, the POSA would at least be able to recognize that a several fold increase in the pemetrexed dose would be needed to maintain the same level of anti-tumor activity as would be needed in an unsupplemented subject. A POSA would have also recognized that the comparison of standard diet mice to the low-folate diet mice was not appropriate due to the administration of an antibiotic to the low-folate diet

mice. A POSA would have likely interpreted these findings as showing a decrease in efficacy of the drug, not just that some therapeutic effects were maintained or that a decrease in lethality permitted higher doses of pemetrexed.

Hammond reports the results of a phase I clinical trial in which patients received 5 mg/day of folic acid starting two days before treatment with pemetrexed at doses ranging from 600 to 925 mg/m^2. TX 912; Ratain Tr. 151:17-22. Out of 33 patients, only one partial response was observed. TX 912. In contrast, the results of an unsupplemented phase I pemetrexed study were published by Rinaldi[4] that showed 4 partial responses and 6 minor responses. TX 1303. Defendants argue that a POSA would have regarded this one partial response as promising and would not have compared it to the results in Rinaldi, and Hammond would have taught a POSA that folic acid supplementation does not decrease pemetrexed's efficacy and does not "teach away" from the claimed invention.

The Court finds that Hammond does meet the legal definition of "teaching away" from the claimed invention or, at the very least, Defendants have not shown by clear and convincing evidence that Hammond would have motivated a POSA to pursue the regimen in Hammond or the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (quoting *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008)) (additional citations omitted). The results of the Hammond study, viewed within the context of the general view that pemetrexed's toxicities were not of great concern to oncologists as of June

[4] Rinaldi, *et al., A phase I evaluation of LY231514, a novel multitargeted antifolate, administered every 21 days*, AMERICAN SOCIETY OF CLINICAL ONCOLOGY, 15:489, Abstract 1559 (TX 1303).

1999, as well as within the context of other pemetrexed studies, including Rinaldi, would not have encouraged a POSA to pursue vitamin supplementation to decrease pemetrexed's toxicity. While it is true that the Hammond study did show that folic acid reduced the toxicity of pemetrexed, a POSA would not have ignored the implications of folic acid supplementation's impact on efficacy. The Hammond study showed only one partial response, as compared to 4 partial responses and 6 minor responses in Rinaldi, and Hammond also involved much higher doses of pemetrexed than what was used in Rinaldi. Even if a POSA would not have made any definitive conclusions about the efficacy of pemetrexed based upon these two phase I studies, a POSA would have compared the results in Rinaldi against the results in Hammond in deciding what impact folic acid supplementation had on the efficacy and toxicity of pemetrexed, and would have selected the regimen that had the most therapeutic benefit, not just some therapeutic benefit.

The Court finds that Lilly's experts, Dr. Chabner and Dr. Zeisel, are more credible with respect to their opinions on how a POSA would view the teachings of Worzalla and Hammond than Defendants' experts. A POSA would not have merely focused on the reduction of toxicity associated with pemetrexed in both of these studies, but would have also looked at the fact that much higher doses of the drug were necessary in order to maintain some antitumor activity. The goal of a POSA would not have been to reduce toxicity at the expense of either reducing the efficacy of pemetrexed or requiring higher doses of the drug, as a POSA would have been concerned with other types of toxicity (such as kidney toxicity) associated with high doses of pemetrexed in humans. Chabner 1318:7-1319:6. Considering that pemetrexed was regarded, as of June 1999, to be a promising antifolate with toxicities that were manageable through dose and schedule modification, Defendants have not shown by clear and convincing evidence that a

POSA would have been motivated to add folic acid supplementation to the administration of pemetrexed based upon the findings in Worzalla and Hammond.

b. '974 Patent as prior art

Defendants argue that the '974 Patent also encourages a POSA to use folic acid supplementation with pemetrexed. The '974 Patent explains that GAR-transformylase ("GARFT") inhibitors and antifolates that bind to the folate binding protein can be administered with folic acid pretreatment to reduce toxicity without affecting therapeutic efficacy; however, the only antifolate specifically mentioned and discussed in the '974 Patent is lometrexol. TX 916 at 1. Defendants argue that this patent could apply to any GARFT inhibitor that binds to the folate binding protein, which would include pemetrexed. Despite the fact that pemetrexed falls within the general class of compounds described in the patent, even Defendants' expert acknowledges that the patent is not directed specifically to pemetrexed, nor is pemetrexed, or the chemical structure of pemetrexed, mentioned anywhere in the patent. Ratain Tr. 302:16-18. In fact, pemetrexed had not even been discovered at the time the '974 Patent was filed, and Defendants' expert stated that a POSA would not have thought the '974 Patent was referring to pemetrexed. Ratain Tr. 302:21- 303:7.

As of June 1999, a POSA would not have concluded that the '974 Patent taught that folic acid supplementation was beneficial to pemetrexed therapy. There is no data in the patent regarding the impact of folic acid on pemetrexed's efficacy, nor could that have even been contemplated by the patent's author at the time it was filed. A POSA would have understood that the focus of the '974 Patent was lometrexol, a drug with a different chemical structure and that was known to have much greater levels of toxicity than pemetrexed. Ratain Tr. 308:12-14. In addition, the POSA would have had access to the Laohavinij article, which indicated that in a study of folic acid supplementation with lometrexol resulted in a fewer number of anti-tumor

responses than had been seen in previously unsupplemented trials with lometrexol, and raised concerns that folic acid could circumvent the anti-tumor activity of lometrexol or aid tumor progression. Ratain Tr. 311:9-312:4; TX 1036 at 333. A POSA would not have looked at the '974 Patent in isolation; rather, he or she would have viewed it in light of the results of the Laohavinij study and would not have been motivated to add folic acid pretreatment to the administration of pemetrexed.

2. Vitamin B_{12} Pretreatment with Pemetrexed was not Obvious

Defendants have not shown by clear and convincing evidence that it would have been obvious to a POSA to add vitamin B_{12} pretreatment to the folic acid pretreatment regimens taught in Worzalla or Hammond to reduce pemetrexed-related toxicity. Defendants assert that the prior art published by Lilly, including the Niyikiza abstracts, taught that nutritional issues contributed to pemetrexed toxicities, and that general knowledge in the art of the association between elevated homocysteine and low levels of both folic acid and vitamin B_{12} would have motivated a POSA to administer B_{12} pretreatment along with folic acid before starting pemetrexed therapy. Defendants further argue that a POSA would have been motivated to add vitamin B_{12} to folic acid pretreatment due to a problem known as "masking" whereby a patient who has a vitamin B_{12} deficiency is misdiagnosed with folate deficiency and treated with folic acid alone, potentially hiding the B_{12} deficiency and leading to neurological damages as a long term effect.

Despite Defendants' claim that the addition of vitamin B_{12} would have been obvious to a POSA, there are no examples in the prior art of cancer patients being pretreated with vitamin B_{12} before being given an antifolate or any suggestion that cancer patients receiving antifolate chemotherapy should receive vitamin B_{12} supplementation. The Niyikiza abstracts teach that there was a strong correlation between elevated homocysteine levels and pemetrexed toxicities;

however, Dr. Niyikiza's initial multivariate analysis indicated that there was not a statistically significant correlation between toxicity and MMA, which is the marker for vitamin B_{12} deficiency. TX 910, 911. Such correlation was not discovered by Dr. Niyikiza until he ran a more extensive statistical analysis of data from patients in the worldwide phase III pemetrexed trial in late 1999, the results of which were not published until June 2002. TX 80. Thus, as of June 1999, a POSA would not conclude from the Niyikiza abstracts that there was a correlation between MMA, indicating B_{12} deficiency, and pemetrexed toxicities. Instead, a POSA would conclude only that there was a correlation between folate deficiency and pemetrexed toxicities. Ratain Tr. 292:5-13. Based upon the Niyikiza abstracts, a POSA would have concluded that vitamin B_{12} deficiency was not the problem in pemetrexed toxicity in June 1999.

Defendants argue that prior art from other disciplines teach that lowering homocysteine levels is achieved by the administration of both folic acid with vitamin B_{12}, and argues that the POSA would have added vitamin B_{12} to the folic acid pretreatment in Hammond and Worzalla to prevent "masking." Defendants argue that the POSA would have administered B_{12} along with folic acid as a safeguard for patients misdiagnosed as folate-deficient, even though they are actually B_{12} deficient, because prolonged B_{12} deficiency could result in neurological damage. Green Tr. 401:9-25. Defendants point to studies by Dr. Morgan in which she routinely administered vitamin B_{12} and folic acid to RA patients on methotrexate therapy to prevent masking of a vitamin B_{12} deficiency. Morgan Tr. 603:11-604:7. However, a POSA would take into account that the studies conducted by Dr. Morgan, as well as the other nutritional science literature cited by Defendants, were not within the context of treating cancer patients. Although Dr. Morgan stated that she had no concerns about giving B_{12} with folic acid to her RA patients and was not concerned about their effect on the efficacy of methotrexate therapy (Morgan Tr. 605:1-5), the POSA would realize that the treatment mechanism of antifolates in RA patients is

different from the mechanism used to treat a cancer patient. Thus, while a rheumatologist would not be concerned with folic acid's and vitamin B_{12}'s interference with the antiproliferative effects of an antifolate in RA patients through an increase in folic acid in the patient's cells, an oncologist would be concerned with interfering with an antifolates' antiproliferative effects because antiproliferation is the means by which the drug kills cancer cells.

In addition, neurological damage would have been less of a concern to the POSA treating cancer patients than it would be in treating RA or cardiovascular patients. First, neurotoxicity from B_{12} deficiency, while a potentially serious condition, is very rare, and arguably not a clinical concern for even RA patients. Zeisel Tr. 1387:6-18. Second, neurotoxicity caused by B_{12} deficiency is chronic and progresses slowly over a period of years, while cancer progresses much faster and is lethal if untreated, or if it is not treated effectively. Zeisel Tr. 1577:8-19. Cancer patients are treated for a relatively short period of time as compared to RA or cardiovascular patients, as these are chronic conditions that are often treated for years on end—in some cases, "greater than 20 years." Cupps Tr. 1386: 12-18. Thus, in RA and cardiovascular patients there would be more concerns about masking due to the extended period of treatment as compared to the duration of anti-cancer therapy. Third, cancer patients see their oncologists at very frequent intervals and are monitored for neuropathy among many other potential toxicities, thus there is a very low likelihood that neuropathy would go unnoticed or untreated. Zeisel Tr. 1572:23-1573:20. Finally, it is important to note that the level of "elevation" of homocysteine levels that Dr. Niyikiza correlated with pemetrexed toxicities was not a clinical elevation and was still within the "normal" range for these patients. Niyikiza Tr. 715:21-716:2. Many of the patients identified by Dr. Niyikiza as having a high likelihood of developing pemetrexed related toxicities would not have been considered medically deficient in either folic acid or vitamin B_{12}, assuming such deficiencies were the actual cause of the "elevated" homocysteine levels, so

neurological damage from a vitamin B_{12} deficiency would not have been a concern in treating these cancer patients. The Court finds that the POSA would place greater priority on treating a patient's cancer over a theoretical concern about neurotoxicity from a B_{12} deficiency, and would not have been motivated to add vitamin B_{12} to a folic acid supplementation regimen based upon prior art in the area of rheumatology or nutritional science.

A POSA would have been further discouraged from adding vitamin B_{12} to the regimens in Hammond and Worzalla based upon what was known in the art about the interaction between B_{12} and folate status. In patients who are vitamin B_{12} deficient, folate becomes "trapped" in cells in the form of 5-methyltetrahydrofolate, which is a form of folate that cannot be used by cells to make DNA. Green Tr. 453:8-15. If such a patient is administered vitamin B_{12}, this "releases" the folate from the "trap" and substantially increases the folate pools available in the individual's cells. Green Tr. 454:9-17. As of June 1999, the POSA would have expected that vitamin B_{12} would counteract the efficacy of antifolates by increasing the production of a critical folate enzyme, methionine synthase, making more folate available to the cell. TX 2093; Green Tr. 454:5- 455:13; Zeisel Tr. 1617:3-13. Even if a POSA were to conclude from the prior art that patients receiving pemetrexed therapy should be treated for both folate and vitamin B_{12} deficiency if they have elevated homocysteine levels, he or she would be concerned about an increase in folate in the patient's cells not just from one source—the folic acid supplementation—but two sources when factoring in the amount of usable folate that would be released by the administration of vitamin B_{12}. For the same reasons a POSA would have been concerned about administering folic acid with pemetrexed, *i.e.* a reduction of efficacy of the antifolate, he or she would have also been concerned with the potential for an even greater amount of folate with the administration of vitamin B_{12} available to compete with the antifolate. *See* TX 915 (risk of progressive malignant tumor growth listed as contraindication for vitamin

B_{12} due to action of B_{12} on tissue growth at high cell multiplication rates). The concern of reducing the efficacy of pemetrexed and potentially encouraging tumor growth would have been of more concern to the POSA than reducing pemetrexed's relatively manageable toxicities or theoretical concerns about "masking" a vitamin B_{12} deficiency with the administration of folic acid alone.

Based upon the forgoing, the Court finds that, as of June 1999, it would not have been obvious for the POSA to add vitamin B_{12} to the folic acid pretreatment with pemetrexed therapy. The POSA would have been more concerned with the impact of vitamin B_{12} on available folate pools in cancer patients and the resulting reduction in efficacy of pemetrexed than he or she would have been with preventing "masking" of a vitamin B_{12} deficiency by not administering vitamin B_{12}.

3. The Doses and Schedules of the Asserted Claims are not Obvious

Defendants argue that the particular doses and schedules of the Asserted Claims do not confer any novelty to the claims because they are (1) arbitrary, and (2) a POSA would have been able to determine the appropriate dose and schedules for folic acid and vitamin B_{12}. The claim that the dose and schedule limitations are arbitrary is not factually sound. Defendants state that the relationship between efficacy and toxicity is the same regardless of whether it is given with the vitamin dosing regimens in the prior art, specifically Hammond and Worzalla, or the claimed vitamin regimen in the '209 Patent. However, the evidence shows that the vitamin dosing regimens in the prior art, which contained folic acid only, reduced the efficacy of pemetrexed as compared to unsupplemented trials, while the regimen in the '209 Patent actually improved the efficacy of the drug over unsupplemented clinical trials. Niyikiza Tr. 825:10-20; TX 2158. This change in the dosage resulted in "unexpectedly good" results achieved at the amounts specified in the '209 Patent. *See Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir.

1989) ("Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. . . . Patentability may be imparted, however, if the results achieved at the designated concentrations are 'unexpectedly good.'") (additional citations omitted). Thus, the Court finds that the doses and schedules in the '209 Patent are not arbitrary.

Defendants make contradictory arguments regarding the obviousness of the dosage and schedules in the Asserted Claims. First, Defendants argue that the therapeutic index of pemetrexed is the same regardless of whether it was given with the vitamin dosing regimen in Hammond—5 mg/day starting two days before and continuing two days after—or whether the regimen in the '209 Patent was used. Dkt. 331 at 41. Then Defendants go on to argue that the POSA would have been motivated to lower the folic acid dosage from that in Hammond because of a theoretical concern that the higher doses of folic acid in Hammond could reduce pemetrexed's efficacy, after previously arguing that the POSA would have no such concern. Dkt. 331 at 23 ("[A] POSA would not have thought that the folic acid pretreatment regimen in Worzalla or Hammond decreased the efficacy of pemetrexed."); Dkt. 331 at 32 ("[A] POSA may have had a theoretical concern that the higher dose of folic acid in Hammond could reduce pemetrexed's efficacy.") (citing Ratain Tr. 208-09). If the POSA would, as Defendants initially argued, have had no concerns regarding the reduction of efficacy of pemetrexed using the Hammond regimen, there would have been no motivation to lower the amounts of folic acid used in the Hammond regimen, thus making the dosing and schedule in the '209 Patent not obvious. Regardless of the Defendants contradictory arguments, the Court finds that the doses and schedules of folic acid (and vitamin B_{12} for the reasons stated above) in the '209 Patent were not obvious.

Defendants also argue that the dosage of folic acid was disclosed in prior art, and are therefore obvious. "A *prima facie* case of obviousness typically exists when the ranges of a

claimed composition overlap the ranges disclosed in the prior art." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)). The range disclosed in the '974 Patent is 0.5 mg to 30 mg (500 µg to 30,000 µg) of folic acid, while the range in the '209 Patent is 350 µg to 1000 µg (0.35 mg to 1 mg). While there is some overlap in the ranges of folic acid doses, the overall claimed composition is different from what is stated in the '974 Patent. As previously discussed, the '974 Patent is focused on use of folic acid pretreatment with lometrexol, which is a different chemical composition and has a different toxicity profile than pemetrexed, a fact a POSA would have been aware of in June 1999. There is no prior art in which the range of folic acid claimed in the '209 Patent is used with pemetrexed. The only prior art references that use folic acid with pemetrexed in clinical trials is Hammond, which used doses of 5 mg, five times the maximum dosage of folic acid in the '209 Patent.

With regard to the obviousness of the dose of vitamin B_{12} in the '209 Patent, there are no prior art references where any amount of vitamin B_{12} pretreatment had been used with an antifolate in the treatment of cancer. Defendants argue that the doses of folic acid and vitamin B_{12} sufficient to lower homocysteine levels are found in literature outside the field of oncology, but this fails to take into account, as previously discussed, that (1) B_{12} deficiency had not yet been determined to be a factor contributing to pemetrexed toxicity as of June 1999; (2) a POSA would have been more concerned about the potential decrease in efficacy from the increase of available folate through the administration of vitamin B_{12} in combination with folic acid than with the theoretical problem of "masking;" and (3) it had been stated in the prior art that administration of vitamin B_{12} was not recommended with antifolates because it could counteract efficacy of antifolates and/or encourage tumor growth. Where a defendant urges an obviousness finding by "merely throw[ing] metaphorical darts at a board" in hopes of arriving at a successful

result, but "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," courts should reject "hindsight claims of obviousness." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (additional citations omitted). Because there is no indication in the prior art of what amount of B_{12} would be successful in the treatment of cancer patients, nor any indication that vitamin B_{12} deficiency was a contributing factor to pemetrexed toxicity as of June 1999, the dose of vitamin B_{12} described in the '209 Patent would not have been obvious to a POSA.

With regard to the dosing schedule for folic acid in the '209 Patent, Defendants have failed to show by clear and convincing evidence that claim 19's requirement that folic acid be administered 1 to 3 weeks prior to pemetrexed would have been obvious. Defendants assert that the '974 Patent discloses that folic acid pretreatment can begin "for periods up to weeks before treatment" to load the folate binding protein, thus it would have been obvious for a POSA to start pretreatment a week or more prior to pemetrexed therapy. TX 916 at 6:30-33. However, the '974 Patent goes on to state that the preferred embodiment of the invention would be to administer folic acid 1 to 24 hours prior to administration of lometrexol, which is outside of the range specified in the '209 Patent. TX 916 at 6:37-42. As has been previously stated, the '974 Patent does not contemplate the use of folic acid with pemetrexed, and lometrexol has a different chemical composition than pemetrexed. Even if a POSA would have thought to attempt to administer folic acid one to three weeks prior to the administration of pemetrexed based upon the '974 Patent, he or she would have considered the results of the Laohavinij prior art along with the '974 Patent, which showed that administration of folic acid one week prior to the administration of lometrexol reduced the efficacy of the drug and was a cause of concern for oncologists. *See* TX 1036 at 333 ("One cause for concern is that the administration of folic acid

prior to lometrexol and during treatment could potentially supplement the folate requirements of the tumor, and thereby circumvent the activity of lometrexol, or worse still, aid tumor progression."). Based upon the results of this study, a POSA would have likely been dissuaded from adding even more folic acid by beginning pretreatment one to three weeks prior to administration of pemetrexed and would not have anticipated a likelihood of success.

With regard to the schedule for administering vitamin B_{12} with pemetrexed, there is nothing in the prior art that would have given the POSA guidance on the dosing schedule specified in the '209 Patent. As of June 1999, there was no confirmed correlation between vitamin B_{12} deficiency and pemetrexed-related toxicities, so the literature from other disciplines relating to treatment of vitamin B_{12} deficiency would not have been helpful to a POSA. In addition, this information would not have given a POSA guidance on how frequently vitamin B_{12} should have been administered to a cancer patient undergoing pemetrexed therapy. The Court finds that the schedule of administration of vitamin B_{12} in the '209 Patent would not have been obvious to a POSA based upon the prior art.

Based upon the forgoing, the Court concludes that the claims covering the dosage and schedules of folic acid and vitamin B_{12} in the '209 Patent are not obvious.

4. Secondary Considerations and Objective Indicia of Non-obviousness of the Asserted Claims

The final factor the Court must consider in making a determination on the issue of obviousness is evidence of secondary considerations and objective indicia of non-obviousness. "Secondary considerations of non-obviousness include the commercial success of the invention at issue and its satisfaction of a long-felt need." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). Other secondary indications of non-obviousness are skepticism or disbelief before the invention and failure of others. *Brown & Williamson Tobacco*

Corp. v. Philip Morris Inc., 229 F.3d 1120, 1129 (Fed. Cir. 2000) (citing *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697–98 (Fed. Cir. 1983)); *Graham*, 383 U.S. at 17. Based upon the evidence presented at trial, secondary considerations support a finding of non-obviousness of the Asserted Claims in the '209 patent.

a. Evidence of skepticism

First, Lilly presented evidence that Dr. Niyikiza's ideas regarding vitamin supplementation with pemetrexed were initially met with skepticism, and only when threatened with the prospect of discontinuation of the phase III clinical trials due to an increase in drug related deaths did Lilly agree to use his protocol. A panel of leading antifolate experts retained by Lilly to provide objective advice on its antifolate development program consistently rejected Dr. Niyikiza's vitamin supplementation protocol, including Antifolate Advisory Panel member Dr. Hilary Calvert. Calvert Dep. Tr. 125:15-25; 126:16-127:12; 133:5-10. Furthermore, the FDA expressed skepticism about adding folic acid pretreatment to the phase III pemetrexed mesothelioma clinical trial, even after Lilly had provided a rationale and support for its proposed protocol change. Defendants argue that Lilly cannot rely upon the FDA "doing its job in regulating safety and efficacy of drugs before they are approved" as evidence of skepticism. Dkt. 331 at 52; *see Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("[R]equest [for clinical safety data and data demonstrating efficacy benefits] reflects attention to the FDA's normal duties ensuring the safety and efficacy of new drugs by requiring actual data to corroborate statements in a new drug application.") The evidence from the FDA that Lilly cites is not merely a request for additional information regarding safety and efficacy; it is a response by the FDA following the submission of requested information on safety and efficacy that indicated that the FDA did not support the proposed plan to add vitamins to the phase III trial. TX 2100; TX 2012 at 2 ("The addition to vitamins to the pivotal trial(s) is

at Lilly's risk."). The Court finds that there was sufficient evidence of skepticism of the claimed invention to support a finding of non-obviousness.

b. Evidence that other attempts had failed

Second, Lilly presented evidence that other attempts at folic acid supplementation with antifolate therapy had failed. "[T]here can be little better evidence negating an expectation of success than actual reports of failure." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012) (quoting *Boehringer Ingelheim Vetmedica, Inc. v. Schering–Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)). The prior art shows that previous attempts at folic acid supplementation with antifolates reduced toxicity, but at the expense of the drugs' efficacy, for both lometrexol and pemetrexed. Calvert Dep. Tr. 129:3-15 (discussing ameliorating toxicity of lometrexol with folic acid, but also eliminating efficacy); TX 912 (Hammond study showed folic acid allowed for dose escalation, but had only one partial antitumor response). Thus, the Court concludes that evidence of other failed attempts supports a finding of non-obviousness.

c. Evidence of unexpected properties

Third, Lilly presented evidence that the '209 Patent resulted in unexpected properties. One way of demonstrating non-obviousness "is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "An invention's unexpected positive properties support the conclusion that the invention would not have been obvious." *Eli Lilly & Co. v. Sicor Pharm., Inc.*, 705 F. Supp. 2d 971, 1007 (S.D. Ind. 2010) *aff'd*, 426 F. App'x 892 (Fed. Cir. 2011).

The Court agrees with Lilly's expert, Dr. O'Dwyer, who testified that the regimen of administering pemetrexed according to the methods that are claimed in the '209 Patent exhibited

properties that would have been unexpected to the POSA in June 1999. O'Dwyer Tr. 1473:16-1474:22. A POSA would have expected the regimen covered in the '209 patent to not only reduce toxicity over unsupplemented administration of pemetrexed, but also reduce the efficacy. O'Dwyer Tr. 1474:14-16. The evidence also demonstrates not only that anti-tumor response was maintained with the vitamin regimen in the '209 Patent, but was actually increased. Niyikiza Tr. 845:4-17; TX 2158; TX 2113 (patients in phase II pemetrexed study with folic acid and B_{12} supplementation were able to receive more cycles of treatment). As of June 1999, a POSA would not have expected an increase in the antitumor activity of pemetrexed with the regimen covered under the '209 Patent, and therefore supports a finding of non-obviousness.

For the reasons set forth above, the Court concludes that the Defendants have not shown by clear and convincing evidence that the '209 Patent is invalid for obviousness under 35 U.S.C. § 103.

5. The Asserted Claims are not Invalid for Obviousness-Type Double Patenting

Defendants assert that the '209 Patent is invalid for obviousness-type double patenting based upon Lilly's expired '974 Patent. "The doctrine of obviousness-type double patenting is intended to 'prevent the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent.'" *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012) (quoting *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985)). The issue of obviousness-type double patenting requires assessing whether, starting with the earlier claim and in light of the prior art, the POSA would have had reason to arrive at the claimed invention. This requires a two-step process. First, the Court must construe the claim in the earlier patent and the claim in the later patent and determine the differences. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (citing *Georgia–Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326, (Fed. Cir.

1999)). Second, the Court must determine whether the differences in subject matter between the two claims render the claims patentably distinct. *Id.* Specifically in this case, the Court must determine whether the Asserted Claims in the '209 Patent are obvious variants of claim 20 of the '974 Patent. Claim 20 of the '974 Patent claims a method for reducing toxicity of a GARFT inhibitor or other antifolate which binds to a folate binding protein in a mammal which comprises pretreating the mammal with about 0.5 mg to 30 mg of folic acid about 1 to about 24 hours prior to administration of the antifolate. TX 916.

a. The Asserted Claims are patentably distinct

The Asserted Claims of the '209 Patent differ from claim 20 in the '974 Patent in that the Asserted Claims limit the drug to pemetrexed and the administration to a patient, use a dose range for folic acid of 350-1000 µg or 350-600 µg and adds vitamin B_{12}, whereas claim 20 of the '974 Patent discloses the use of a much greater amount of folic acid—500-30,000 µg—with an antifolate that inhibits GARFT or binds to a folate binding protein binding agent administered to a mammal. The '974 Patent does not reference pemetrexed or contain any data about pemetrexed; rather, it covers a very broad class of compounds by specifying properties that virtually every antifolate shares, but the background section of the patent states that lometrexol is the focus of the patent. Ratain Tr. 296:12-297:17; TX 916 at 1. There is also nothing in the '974 Patent regarding pretreatment with vitamin B_{12}.

The Court finds that as of June 1999, it would not have been obvious for a POSA to select pemetrexed for use with claim 20 of the '974 Patent. Defendants argue that a POSA would have selected pemetrexed to use with claim 20 of the '974 Patent because it was a very promising antifolate in June 1999. However, a POSA would have known that pemetrexed had a different toxicity profile than lometrexol, and, as previously discussed, the results of Hammond and Worzalla would not have motivated a POSA to use pemetrexed with this treatment regimen

and risk decreasing the efficacy of this very promising drug that, unlike lometrexol and the '887 compound, was regarded as having manageable toxicities. Also as previously discussed, there would have been no reason for a POSA to add vitamin B_{12} to the folic acid pretreatment, as there was no data on the use of vitamin B_{12} pretreatment with pemetrexed, and a correlation between B_{12} deficiency and pemetrexed toxicity had not yet been established in the prior art.

Defendants also assert that the overlap of dose ranges for folic acid specified in the '974 Patent and the '209 Patent creates a presumption of obviousness. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006). However, "[t]he presumption can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results." *Id.* As discussed above, the claimed ranges of folic acid and vitamin B_{12} did produce new and unexpected results, as the regimen had a positive effect on efficacy instead of having the negative effect seen in other studies such as Hammond, Worzalla, and Laohavinij. For this reason, the Court concludes that the dosages specified in the '209 Patent are patentably distinct.

Finally, a POSA would not have arrived at the dosing schedule in the '209 Patent based upon claim 20 of the '974 Patent. The Asserted Claims of the '209 Patent specify that folic acid is to be administered 1 to 3 weeks prior to the first pemetrexed treatment, and vitamin B_{12} is to be administered 1 to 3 weeks prior to treatment with pemetrexed, then once every 6 to 12 weeks, while claim 20 of the '974 Patent specifies that folic acid is to be administered 1 to 24 hours before treatment with an antifolate. There is no overlap between the dosing schedules of the '209 Patent and the '974 Patent, and thus no presumption of obviousness.

For these reasons, the Court finds that the Asserted Claims in the '209 Patent are not invalid for obviousness-type double patenting.

6. The Asserted Claims Satisfy the Requirements Under 35 U.S.C. § 112

Defendants assert that lack of written description and lack of enablement render the '209 Patent invalid. 35 U.S.C. § 112 states that patents "shall contain a written description of the invention" and the first paragraph of § 112 contains two separate description requirements: a "written description [i] of the invention, *and* [ii] of the manner and process of making and using [the invention]." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (quoting 35 U.S.C. § 112, ¶ 1) (emphasis in original).

1. Adequate Description of Asserted Claims

The written description is a statutory requirement set forth in 35 U.S.C. § 112, which states that a patent "must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Realtime Data, LLC v. Morgan Stanley*, No. 2013-1103, 2014 WL 278757, at *9 (Fed. Cir. Jan. 27, 2014) (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)).

Defendants have not shown by clear and convincing evidence that the Asserted Claims in the '209 Patent are not adequately described. Defendants argue that the requirement of the use of "an effective amount of pemetrexed" with folic acid and vitamin B_{12} pretreatment is insufficient because the specification does not describe a particular dose of pemetrexed to be given with folic acid and vitamin B_{12}. The specification discloses using the pretreatment regimen *in combination with* an "effective amount" of pemetrexed, not an amount of pemetrexed that would be effective if combined with vitamin pretreatment, as argued by the Defendants. TX 1 at 3 *ll*. 3-4. The Court and the parties have defined an "effective amount of pemetrexed" as the amount that is "capable of providing a therapeutic benefit to the patient in need thereof." Dkt. 110 at 2. A POSA who is an oncologist or who has worked with oncologists would be able to determine what an "effective amount of pemetrexed" would be, prior to adding the vitamin

pretreatment, and then combine this amount with the vitamin regimen in the '209 Patent; the specification does not require the POSA to determine what dose and schedule of pemetrexed would be effective dependent upon combination with the vitamin pretreatment. "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010); *see also LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) ("[T]he patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. . . . Placed in that context, it is unnecessary to spell out every detail of the invention in the specification.").

The Court concludes that a POSA would know, based upon the prior art, what amount of pemetrexed constitutes an "effective amount," and would have no difficulty in understanding what invention Dr. Niyikiza described or that he was in possession of the idea of using such an amount of pemetrexed in his invention. O'Dwyer Tr. 1449:13-1450:19. Therefore, the Court concludes that the written description requirement of 35 U.S.C. § 112 is satisfied.

2. Enablement of Asserted Claims

Defendants have also not shown by clear and convincing evidence that the '209 Patent does not provide adequate information to enable the claims. The enablement requirement is met when "at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (quoting *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)).

The following factors, known as the "*Wands* factors," may be considered when determining if a disclosure requires undue experimentation:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Cephalon, Inc. v. Watson Pharm., Inc., 707 F.3d 1330, 1336 (Fed. Cir. 2013) (quoting *Wands*, 858 F.2d at 737). Because the adequacy of the disclosure is judged from the perspective of one of ordinary skill in the art, the POSA may rely on what is known in the art to practice the invention, and it is not necessary for the patent specifications to disclose precisely how to make and use the invention. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006).

The Court has already determined that a POSA for purposes of this litigation is a medical doctor who specializes in oncology or a medical doctor with experience in the areas of nutritional science involving vitamin deficiencies who has collaborated with medical oncologists with knowledge and experience in the treatment of cancer through the use of antifolates. Dkt. 115 at 8. A POSA would have had access to prior art references that disclosed effective amounts of pemetrexed that would at least provide a starting point for practicing the invention. *See* TX 78 at 1195 (phase II pemetrexed study stating "recommended starting dose for phase II studies . . . was 600 mg/m^2."); TX 1151 (phase II study utilizing 500-600 mg/m^2 doses of pemetrexed in treatment of various cancer types); TX 1152 at 196-197 (discussing phase II study using 500-600 mg/m^2 doses of pemetrexed). "[G]iven the ready accessibility of the journals, the absence of incorporation by reference is not problematic. Indeed, '[a] patent need not teach, and preferably omits, what is well known in the art.'" *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (quoting *Spectra–Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)). Based upon the specificity of the numerous prior art references available to a POSA at the time of the filing of the '209 Patent application that provide data regarding the amount of pemetrexed capable of producing a therapeutic benefit, the Court concludes that he or she would

not need to engage in undue experimentation to reach an "effective amount" of pemetrexed to be used with the Asserted Claims. For these reasons, the Court concludes that the Asserted Claims satisfy the enablement requirement of 35 U.S.C. § 112.

The Court concludes that the Asserted Claims of the '209 Patent satisfy the requirements of 35 U.S.C. § 112 and thus are not invalid for inadequate description or lack of enablement.

III. CONCLUSION

Based upon the forgoing findings of fact and conclusions of law, the Court concludes that the Defendants have failed to show by clear and convincing evidence that the Asserted Claims of the '209 Patent are invalid for obviousness, obviousness-type double patenting, inadequate description or lack of enablement. Therefore, the Court finds that the Asserted Claims of the '209 Patent are valid and enforceable, and enters judgment in favor of Eli Lilly and against Defendants. Final judgment shall be entered accordingly.

SO ORDERED.

Date: 03/31/2014

Hon. Tanya Walton Pratt, Judge
United States District Court
Southern District of Indiana

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