No. 2018-2128

United States Court of Appeals for the Federal Circuit

ELI LILLY & CO.,
Plaintiff-Appellee,

v.

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC.,
Defendants-Appellants.

Appeal from the U.S. District Court for the Southern District of Indiana, No. 1:16-cv-00308-TWP, Judge Tanya W. Pratt

APPELLANTS' OPENING BRIEF
(Non-Confidential Version)

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October 9, 2018

U.S. Patent No. 7,772,209 Claim 12 (Appx53, emphasis added)

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

a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;

b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium.

CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants certify the following:

1. Full name of Party Represented by us:	**2. Name of any Real Party in Interest not identified in response to Question 3:**	**3. Parent corporations and publicly held companies that own 10% or more of the stock in the party:**
Dr. Reddy's Laboratories, Inc.	None.	Dr. Reddy's Laboratories, S.A. Dr. Reddy's Laboratories, Ltd.
Dr. Reddy's Laboratories, Ltd.	None.	None.

4. The names of all law firms and the partners or associates who appeared for the party now represented by us in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Harrison & Moberly: Charles E. Oswald, Rory O'Bryan, Stephen E. Arthur

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal, per Fed. Cir. R. 47.4(a) and 47.5(b):

Eli Lilly and Co. v. Hospira, Inc., No. 18-2126 (Fed. Cir.)

Eli Lilly and Co. v. Hospira, Inc., No. 1:16-cv-03460 (S.D. Ind.)

Eli Lilly and Co. v. Actavis LLC, No. 1:17-cv-00982 (S.D. Ind.)

Eli Lilly and Co. v. Apotex, Inc., No. 1:17-cv-02865 (S.D. Ind.)

Eli Lilly and Co. v. Eagle Pharms., Inc., No. 1:17-cv-01293 (D. Del.)

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Note re: Confidential Material

Material redacted at pages 6 and 15 of the non-confidential version of this brief, and highlighted in the confidential version, quotes or summarizes details of provisions of a confidential agreement between Eli Lilly & Co. and a non-party. The referenced provisions were marked confidential in the proceedings below under the terms of the governing protective order, and were not, to counsel's knowledge, revealed in proceedings open to the public.

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Note: All quoted emphasis is added unless otherwise indicated.

STATEMENT OF RELATED CASES

No appeal has previously been taken from the proceedings below. The following pending cases involve the same patent at issue here, and may affect or be affected by the decision in this appeal: *Eli Lilly & Co. v. Hospira, Inc.*, No. 18-2126 (Fed. Cir.); *Eli Lilly & Co. v. Hospira, Inc.*, No. 1:16-cv-03460 (S.D. Ind.); *Eli Lilly & Co. v. Actavis LLC*, No. 1:17-cv-00982 (S.D. Ind.); *Eli Lilly & Co. v. Apotex, Inc.*, No. 1:17-cv-02865 (S.D. Ind.); and *Eli Lilly & Co. v. Eagle Pharms., Inc.*, No. 1:17-cv-01293 (D. Del.).

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331, 1338(a). The district court entered final judgment on June 22, 2018. Appx7-8. Appellants ("Dr. Reddy's") timely filed a notice of appeal on June 29, 2018. Appx4265-4267. After resolving Eli Lilly's Rule 59(e) motion to amend the final judgment, Appx2-6, the district court entered an amended final judgment on July 27, 2018. Appx1. Dr. Reddy's timely filed an amended notice of appeal on August 1, 2018.

This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

PRELIMINARY STATEMENT

The district court's judgment rests on a fundamental misapplication of the doctrine of equivalents at nearly every step. The doctrine of equivalents is "premised on language's inability to capture the essence of innovation." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002). Where a patentee "lacked the words to describe" an alleged equivalent during prosecution, *id.*, the patentee may rely on the doctrine of equivalents in litigation. Even then, however, the doctrine remains subject to the background principle that a patent's claims and prosecution history serve important public notice functions. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129-30 (2014); *Schriber-Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 220-21 (1940); *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966). Indeed, the Supreme Court has cautioned that the doctrine should not "take[] on a life of its own, unbounded by the patent claims." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28-29 (1997). A patentee "should know what he owns, and the public should know what he does not," even accounting for equivalents. *Festo*, 535 U.S. at 731.

The doctrine of equivalents is thus not a mulligan or a second chance for patentees who come to regret choices they made in prosecution when later faced with a competitor who designed around the literal scope of the claims. This Court has consistently rejected buyer's-remorse arguments from patentees who contend that prosecution history estoppel should not apply because they gave up more claim scope than they needed to avoid prior art.

In this case, the district court made three critical errors in applying the doctrine of equivalents. Each is an independently sufficient reason to reverse. All three allowed Lilly to broaden its claims in litigation to cover subject matter that its competitors were entitled to believe Lilly had relinquished. *First*, the district court's treatment of prosecution history estoppel causes the narrow tangential exception to swallow the general rule. It fails to account for Lilly's specific choice to claim "pemetrexed disodium" rather than "antifolates"—and rather than any other (broader) subset of "antifolates." Worse, it allows Lilly to do exactly what this Court has repeatedly held patentees may not do: avoid disclaimer or estoppel by arguing that they gave up more than they needed to avoid prior art. *Second*, in contrast to its erroneously broad

view of the tangential exception, the district court relied on an erroneously narrow conception of the disclosure-dedication rule, which would effectively require incorporation by reference for subject matter to be deemed disclosed. The district court's approach fails to account for Lilly's broad disclosure and narrow claiming. *Finally*, the district court's ultimate equivalence analysis disregards Lilly's choice to claim "method[s] for administering" drugs and to cancel claims for "method[s] of inhibiting tumor growth," treating the former as if they claimed the latter.

A proper analysis of prosecution history estoppel's tangential exception, the disclosure dedication rule, *or* equivalence requires rejecting Lilly's doctrine-of-equivalents theory. The judgment of infringement should be reversed.

STATEMENT OF THE ISSUES

I. Lilly's '209 patent originally claimed administration of "an antifolate." During prosecution, Lilly narrowed the original "antifolate" element in its claims to one particular antifolate compound—"pemetrexed disodium." Did the district court err as a matter of law by applying the "tangential" exception to prosecution history estoppel to permit Lilly to

argue that Dr. Reddy's pemetrexed ditromethamine product infringes under the doctrine of equivalents?

II. The '209 patent claims administration of only one antifolate—"pemetrexed disodium." The specification also discloses that other "[p]referred" antifolates include the derivatives described in Akimoto—which describes "pharmaceutically acceptable" "substituted ammonium" salts of pemetrexed. Tromethamine was one of the few FDA-approved substituted ammonium salts when the '209 patent was filed, and had been identified as an alternative to sodium for making drug salts. Did the district court err as a matter of law in concluding that Lilly has not dedicated pemetrexed ditromethamine to the public?

III. The '209 patent's specification distinguishes "method[s] of inhibiting tumor growth" from "method[s] for administering" pemetrexed disodium. During prosecution, Lilly abandoned or cancelled claims to the former, while preserving claims to the latter. Did the district court err as a matter of law in concluding that the undisputed chemical differences between the antifolates "administer[ed]" in Dr. Reddy's method (pemetrexed ditromethamine) and the '209 patent's method (pemetrexed disodium) were "irrelevant" to the doctrine of equivalents analysis?

STATEMENT OF THE CASE

Eli Lilly & Co. markets and sells a chemotherapy agent under the brand name ALIMTA, for which the active ingredient is *pemetrexed disodium*. Lilly's U.S. Patent No. 7,772,209 patent recites methods for administering "pemetrexed disodium." Lilly sued Dr. Reddy's for infringement arising out of Dr. Reddy's application for FDA approval to market and sell a competing chemotherapy agent, for which the active ingredient is *pemetrexed ditromethamine*. After a bench trial, the district court concluded that Dr. Reddy's would indirectly infringe the '209 patent under the doctrine of equivalents, and ordered that Dr. Reddy's FDA approval be delayed until after the '209 patent expires. Appx9-22; Appx7-8; Appx1. Dr. Reddy's now appeals.

I. Background

A. Antifolates and Lilly's ALIMTA Product

Lilly's ALIMTA was approved by the FDA in 2004. ALIMTA contains the active ingredient "pemetrexed disodium," which is a salt of the active moiety "pemetrexed." Appx7808-7834. Pemetrexed disodium is in a class of anticancer drugs called antifolates. The first clinically active antifolates were discovered over 60 years ago. Appx48(1:19-21)

(discussing aminopterin). Methotrexate, another antifolate, was developed several decades ago and is widely used today. *Id*. (1:22-25).

Pemetrexed compounds were the subject of extensive research and patenting by others in the 1990s. U.S. Patent Nos. 4,997,838 ("Akimoto") and 5,344,932 ("Taylor"), for example, issued to inventors at Takeda Pharmaceutical and Princeton University, and disclosed groups of antifolate compounds—including pemetrexed compounds—that inhibited tumor growth. *See, e.g.*, Appx7933-7934(1:44-3:17) (Akimoto); Appx4561(249:11-15) (discussing Akimoto); Appx4632-4634(320:25-322:21) (same); Appx8010(1:56-66) (Taylor, referring to tumor cells as "neoplasms").

Lilly took licenses to the Akimoto and Taylor patents. Lilly's license to Akimoto recognized that pemetrexed disodium (referred to in the agreement as "LY213514") [redacted] by [redacted] Appx7907([redacted].

Lilly also took an exclusive license to the Taylor patent, Appx7927-7931; Appx7905(recital 2), and relied on that patent to exclude generic competition with its ALIMTA product. The Taylor patent's claims

broadly covered *any* salt of pemetrexed. Appx8019-8020(claims 1-7); Appx4567-4568(255:3-256:1); Appx4660-4665(348:14-353:7). Before its expiration in 2016, the Taylor patent was listed in the Orange Book for ALIMTA. Appx8009-8022; Appx8092. From approximately 2008 to 2014, Lilly successfully asserted the Taylor patent against several generic competitors. *See, e.g.*, *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368 (Fed. Cir. 2012) (appeal from consolidated, 2008-filed actions against Teva, APP, and Barr); *Eli Lilly & Co. v. Nang Kuang Pharm. Co.*, No. 1:14-CV-1647 (S.D. Ind. filed Oct. 8, 2014).

Lilly began filing its own patent applications relating to ALIMTA in 2001, with U.S. Patent No. 6,686,365. Appx7975-7979. The '365 patent issued in 2004, around when the FDA approved ALIMTA. The '365 patent claims "pharmaceutical composition[s] comprising … *pemetrexed*" in combination with an antioxidant and an excipient. Appx7978(5:19-6:39). The '365 patent's written description states that "[a]s used herein, the term '*pemetrexed*' refers to the stable salts, acids and free base forms thereof," Appx7977(3:10-20), and provides an extensive list of pemetrexed salts.

B. Lilly's U.S. Patent No. 7,772,209

The patent asserted in this case is Lilly's U.S. Patent No. 7,772,209. That patent is a follow-on to Lilly's earlier, broader patents. Just months before the July 2016 expiration of the Taylor patent (which Lilly successfully asserted against generics for several years, *see* §I.A, *supra*), Lilly sued Dr. Reddy's for infringement of the '209 patent. Appx583-592 (filed February 5, 2016). Unlike the '365 patent, the '209 patent's claims require "*pemetrexed disodium*," not "*pemetrexed*," and not "salts, acids, and free base forms thereof." As explained below, the claims were originally not so limited, but were amended in response to rejections.

The '209 patent recites a method for administering pemetrexed disodium with an "FBP binding agent" (such as folic acid) and a "methylmalonic acid lowering agent" (such as vitamin B12). The patent states that certain toxic side effects were reduced when patients took an FBP binding agent and a methylmalonic acid lowering agent before administration of pemetrexed disodium. Appx48(2:32-46). Claim 12 is representative:

> **12.** An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
>
> a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

Appx53.

1. The '209 Patent's Written Description Discloses "Substituted Ammonium" Salts of Pemetrexed as Alternatives to Pemetrexed Disodium.

The '209 patent claims priority to U.S. Patent Application No. 10/297,821, which was filed in 2001. Appx45-54. Initially, Lilly tried to claim broader subject matter, relating to the administration of *any* antifolate.

Consistent with that initial strategy, and relevant to the disclosure-dedication issue in this case, the '209 patent's written description focuses on pemetrexed disodium, but also discloses that "substituted ammonium salts" of pemetrexed are an alternative to the pemetrexed disodium recited in the claims.

The '209 patent's written description states that pemetrexed's sodium salt—"Pemetrexed Disodium (ALIMTA)"—is the "*most preferred*" antifolate. Appx49(4:42-43). The written description singles out other antifolates as "preferred," including antifolates described in Akimoto:

> Preferred examples of antifolates include Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; *derivatives described by Akimoto in U.S. Pat. No. 4,997,838*; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

Appx49(4:34-43). Consistent with the broader practice in the pharmaceutical industry of substituting ammonium salts for sodium salts, at least six of the listed "preferred examples of antifolates" disclose "substituted ammonium salts." Appx7982(3:48-51) (EPO '632 application); Appx7939(14:40-48) (Akimoto); Appx7953(3:15-21) (Taylor '653 patent); Appx7965(3:40-46) (Taylor '145 patent); Appx7970-7971(2:66-3:4) (Taylor '743 patent), Appx8025(3:4-17) (Taylor '334 patent). Indeed, the cross-referenced Akimoto patent is the patent to which Lilly took a license in connection with its development of ALIMTA (as described above). Akimoto specifically describes "pyrrolopyrimidine *derivatives*," including

pemetrexed. Appx7932(title); Appx4561(249:11-15); Appx4632-4634(320:25-322:21). And Akimoto singles out "substituted ammonium" salts as "exemplif[ying] the salts of pharmaceutically acceptable bases" that can form from pemetrexed. Appx7939(14:41-45).

Lilly's expert conceded that "[n]ot every chemically viable salt form can be used for formulating [a pharmaceutical] product, so the subset of possible counterions" for a given active ingredient "is smaller than the overall number" of salts it could form. Appx4550(238:20-22). When the '209 patent was filed, pharmaceutical "formulator[s had] know[n] that for an injectable dosage form of an API like pemetrexed salts, that only a few cations are commonly used to make the salt form." *Id.* (238:17-20). Tromethamine (the cation in pemetrexed ditromethamine) was one of the most commonly used substituted ammonium cations for injectable dosage forms. *See infra* p. 61.

2. Lilly Narrows Its Claims from "Antifolate" to "Pemetrexed Disodium" to Overcome Rejections.

During prosecution of application no. 10/297,821 (the application to which the '209 patent claims priority), Lilly initially claimed methods of administering *any* "antifolate" with vitamin B12 and folic acid. Appx7859-7862. After prior-art-based rejections by the Patent Office and

several amendments, the '209 patent issued with claims narrowly drawn to "method[s] for administering" one specific antifolate: "pemetrexed disodium"—*i.e.*, the active ingredient in ALIMTA. Appx52-53(10:56-12:29).

Lilly filed the '821 application (grandparent to the '209 patent) in June 2001 with the title "Novel *Antifolate* Combination Therapies." Appx7859. After a preliminary amendment, the originally filed independent claims broadly recited methods of administering "an antifolate." Appx7860-7861. For example, original claim 2 read as follows:

> 2. (Original) A method of reducing the toxicity associated with the administration of *an antifolate* to a mammal comprising administering to said mammal an effective amount of said *antifolate* in combination with a methylmalonic acid lowering agent.

Appx7860. Some dependent claims recited that "the antifolate is ALIMTA," which the written description described as "Pemetrexed Sodium … as manufactured by Eli Lilly & Co." Appx7861 (claims 9, 29, 30); Appx7876.

a. The Examiner's Rejections.

The examiner rejected all of Lilly's original claims on multiple grounds of anticipation or obviousness in light of prior art. *First*, a 1978

article ("Arsenyan") anticipated claims that required administration of "an antifolate" in combination with a methylmalonic acid lowering agent. Appx7860-7861. Arsenyan teaches treatments using *methotrexate*, an antifolate. Before administering methotrexate to mammals with cancer, Arsenyan teaches "pretreating" them "with methylcobalamin (a vitamin B12 derivative which reduces methylmalonic acid)," and reports "increased tumor inhibition and survival" with that pretreatment. Appx7868.

Second, the examiner rejected claims as obvious over the combination of a patent (Ohmori) and a 2000 article (John) titled *Activity of multitargeted antifolate (pemetrexed disodium, LY231514) in patients with advanced colorectal carcinoma*. Appx7869-7870. Ohmori teaches a method of administering vitamin B12 and folic acid, but without specifying any drug. Appx7869. John teaches "the toxicities associated with administration of the multitargeted antifolate pemetrexed disodium, … also known by the trade name ALIMTA." *Id.*

Third, the examiner rejected claims as obvious over Arsenyan, Ohmori, and a 1998 article (Worzolla) titled *Role of folic acid in*

modulating the toxicity and efficacy of the multitargeted antifolate, LY231514. Appx7870-7872.

b. Lilly's Amendments.

The examiner's prior-art rejections came in an office action in September 2004, seven months after the FDA had approved ALIMTA. In response, Lilly amended its application in several ways to focus narrowly, and specifically, on *pemetrexed disodium*.

First, Lilly retitled its application, from "Novel *Antifolate* Combination Therapies," to "*Vitamin B12 and Pemetrexed Disodium* Combination Therapies." The revised title, Lilly stated, was "more indicative of the invention." Appx7876; Appx7879.

Second, Lilly cancelled all claims reciting administration of "ALIMTA," Appx7877-7879, and corrected its description of "ALIMTA" in the written description to read "Pemetrexed Disodium," instead of "Pemetrexed Sodium."

Third, critically, Lilly deleted *every* instance of "an antifolate" in the claims, and substituted "pemetrexed disodium." *Id.* Then-amended claim 2 illustrates the substitutions:

> 2. (Currently Amended) A method of reducing the toxicity associated with the administration of ~~an antifolate~~ **pemetrexed disodium** to a ~~mammal~~ human comprising administering to said ~~mammal~~ human an effective amount of ~~said antifolate~~ **pemetrexed disodium** in combination with a methylmalonic acid lowering agent, selected from vitamin B12 or a pharmaceutical derivative thereof.

Id. (bolded colors added). Lilly also added a new independent claim, which likewise recited "pemetrexed disodium." Appx7878.

In narrowing its claims from "antifolate" to "pemetrexed disodium," Lilly bypassed other intermediate options. One option would have been to claim "*pyrrolopyrimidine derivative antifolates*," in those or similar words, or in a similar manner to the Akimoto and Taylor patents that Lilly licensed. Appx7932(title); Appx7933(1:1-12); Appx7952(1:1-33); *cf.* Appx7907([redacted]). The '209 patent's written description uses similar terminology. Appx49(4:37-40) ("pyrido[2,3-d]pyrimidine derivatives described by Taylor et al …" and "derivatives described by Akimoto"). "Pyrrolopyrimidine derivatives" are compounds, like pemetrexed disodium, that contain a "pyrrolopyrimidine" chemical group. The prior art Arsenyan reference refers to methotrexate, which is not a pyrrolopyrimidine derivative. Appx4417-4418(105:19-106:18); Appx4503-4504(191:18-192:2).

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Other options would have been to replace "an antifolate" with "pemetrexed salts" or with "*pemetrexed*"—as Lilly had done with its '365 patent, and as Lilly had tried to do in Europe with the foreign counterpart to the '209 patent. As noted above, the claims of Lilly's '365 patent recite "pemetrexed," and the '365 patent's written description states that "[a]s used herein, the term 'pemetrexed' refers to the stable salts, acids and free base forms thereof," Appx7977(3:10-20), while providing an extensive list of pemetrexed salts.

In prosecution of the European counterpart to the '209 patent, Lilly began (as in the United States) with claims directed to use of "antifolates" generally. Appx1506. In response to rejections, Lilly "refocused on the use of the antifolate compound pemetrexed," *id.*, drafting independent claims reciting "pemetrexed" and dependent claims reciting "pemetrexed disodium." The European Patent Office rejected the broader claims, and only claims to "pemetrexed disodium" ultimately issued.

With the '821 application, however, Lilly amended its claims to recite "pemetrexed disodium," and focused specifically on the claimed "*pemetrexed disodium*" in responding to the examiner's rejections. Lilly stated "[t]he present invention, as defined in the Claims, concerns itself

with the discovery that vitamin B_{12} reduces toxicities associated with the administration of *pemetrexed disodium*." Appx7882. In response to the anticipation rejection, Lilly emphasized, "Arsenyan et. al. does not disclose *pemetrexed disodium* and does not disclose the use of vitamin B_{12} or a pharmaceutical derivative to reduce the toxicity associated with the administration of *pemetrexed disodium*, or for that matter any other antifolate." Appx7880. In response to the obviousness rejections, Lilly similarly argued that no references "suggest[] nor motivate[] the skilled artisan to arrive at the use of vitamin B_{12} to reduce toxicities associated with the administration of *pemetrexed disodium*." *Id.*; *see* Appx7883 (similar); *see generally* Appx7880-7884.

From then on, Lilly continued to prosecute claims limited to "pemetrexed disodium." After further proceedings, the examiner ultimately allowed the claims of the '821 application, which issued as U.S. Patent No. 7,053,065 (grandparent patent to the '209 patent). Appx46(cover); Appx5649-5654. Every claim in that patent refers only to "pemetrexed disodium."

3. Lilly Abandons or Cancels Claims to "Method[s] of Inhibiting Tumor Growth," Leaving Claims to "Method[s] for Administering."

The direct parent application to the '209 patent (No. 11/288,807), was originally filed with claims directed to "method[s] of inhibiting tumor growth." Appx6599 (claims 3, 6, and dependent claims); Appx6616-6617 (claims 3 and 34-40, entered after a preliminary amendment). The examiner rejected these method-of-treatment claims for non-enablement under 35 U.S.C. § 112 "because the specification, while being enabling for inhibiting tumor growth in breast cancer, does not reasonably provide enablement for inhibiting tumor growth caused by other cancers." Appx6674. Lilly abandoned the '807 application without further amendment. Appx6693-6694.

Lilly filed the application leading to the '209 patent as a divisional of the '807 application. Appx46(cover). The '209 patent, like the '807 application, originally included claims to "method[s] of inhibiting tumor growth." Appx5507-5510(claims 3, 6, and dependent claims). In a preliminary amendment, however, Lilly cancelled those claims. The '209 patent issued in 2010. Appx46(cover).

4. The '209 Patent Claims a "Method for Administering" Only One Antifolate—"Pemetrexed Disodium."

Each of the '209 patent's claims requires administration of folic acid and a methylmalonic acid lowering agent, followed by administration of pemetrexed disodium. As noted above, as a result of amendments in prosecution, all claims are drawn to "method[s] for administering pemetrexed disodium." Claim 12, for example, recites:

> **12.** An improved *method for administering pemetrexed disodium* to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
>
> a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first *administration of pemetrexed disodium*;
>
> b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first *administration of pemetrexed disodium*; and
>
> c) *administration of pemetrexed disodium*.

Appx53(11:26-12:4).

Although the specification describes "the present invention" as relating to "a method of administering an antifolate," "a method of reducing toxicity," and "a method of inhibiting tumor growth," consistent with narrowing amendments in prosecution, the *claims* recite only the first of those methods, not the other two. Appx48-49(2:55-3:39). And as Lilly's corporate representative (who supervised the prosecution of the

'209 patent) testified, the reason the '209 patent claimed "pemetrexed disodium" was to "carry[] through the terminology that had been used in the prior parent and divisional application[]," and "[b]ecause the claim was directed to [Lilly's] compound that is the product Alimta." Appx8342-8343(67:17-68:2).

C. Dr. Reddy's Pemetrexed Ditromethamine Product

Dr. Reddy's product does not contain pemetrexed disodium. Instead, it contains the active ingredient pemetrexed ditromethamine, Appx4391(79:23-25), which is a substituted ammonium salt of pemetrexed. Appx4474(162:15-17).

Pemetrexed disodium and pemetrexed ditromethamine are undisputedly different chemicals with different properties. In pemetrexed disodium, the pemetrexed ion is bonded to two sodium atoms. In pemetrexed ditromethamine, the pemetrexed ion is bonded to two tromethamine molecules. Among other things, sodium and tromethamine dissociate from pemetrexed in different ways. Appx4676(364:5-21). The table below lists other differences between the respective ions.

Sodium	**Tromethamine**
Atom	Molecule

Inorganic	Organic
Only electrostatic interactions with water	Electrostatic and hydrogen bonding interactions with water
1/5 the molecular weight of tromethamine	5 times the molecular weight of sodium
No chemical bonds	Nineteen chemical bonds
Metal	Nonmetal
Not a base	Base
No buffering capacity	Buffering capacity
Not a pH adjuster	pH adjuster

Appx4673-4676(361:18-364:24).

Moreover, as compared to pemetrexed disodium, pemetrexed ditromethamine: **(1)** requires 1.4 times as much weight of the salt to administer the same amount of pemetrexed active moiety, **(2)** is 4 times more soluble, and **(3)** is half as hygroscopic. *See* Appx4493(181:4-25); Apxx4673-4676(361:18-364:24).

Because Dr. Reddy's active ingredient (pemetrexed ditromethamine) differs from the active ingredient in Lilly's ALIMTA (pemetrexed disodium), Dr. Reddy's submitted a New Drug Application to the FDA under 21 U.S.C. §355(b)(2), not an ANDA under 21 U.S.C. §355(j).

II. District Court Proceedings

Lilly sued Dr. Reddy's in district court, asserting infringement of the '209 patent. At trial, Lilly only asserted indirect infringement under the doctrine of equivalents. Dr. Reddy's did not contest validity, and Lilly did not contend that Dr. Reddy's literally or directly infringed. *See* Appx4321(9:11-18).

Three of Dr. Reddy's noninfringement arguments are relevant to this appeal. *First*, Dr. Reddy's relied on prosecution history estoppel. Because Lilly had narrowed its claims in prosecution from "antifolate[s]" to "pemetrexed disodium" in response to prior-art rejections, Lilly could not rely on the doctrine of equivalents to assert its patent against "antifolate[s]" other than "pemetrexed disodium." *Second*, Dr. Reddy's relied on the disclosure-dedication rule. Because Lilly's patent disclosed "substituted ammonium" salts like pemetrexed ditromethamine as "preferred" alternatives, *see supra* §I.B.1, but only claimed methods for administering pemetrexed disodium, *supra* §I.B.4, methods for administering pemetrexed ditromethamine are dedicated to the public. *Finally*, Dr. Reddy's contested equivalence, noting that Lilly had claimed only "method[s] for *administering*" pemetrexed disodium, while disclaiming or

abandoning methods of treatment or reducing toxicity. Regardless of similarities between the compounds for other purposes, pemetrexed ditromethamine was not an "equivalent" of pemetrexed disodium for purposes of the '209 patent's claims.

A. The District Court's Ruling That Prosecution History Estoppel Does Not Bar Lilly From Relying on the Doctrine of Equivalents

Under the doctrine of prosecution history estoppel, a patentee cannot surrender literal claim scope in prosecution to obtain its patent, and later use the doctrine of equivalents in litigation to recapture that scope. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1365 (Fed. Cir. 2003) (en banc). The district court held—in denying summary judgment and in adjudicating Lilly's claims at trial—that prosecution history estoppel did not apply because Lilly's amendments fit into the "tangential" exception to that rule, articulated in *Festo*, 535 U.S. at 740-41. Appx34-37; Appx12-13.

The court noted that "[i]t is undisputed that Lilly narrowed its broader antifolates claim to pemetrexed disodium during prosecution to avoid Arsenyan prior art" and that "Dr. Reddy's product would fall within the scope of the original antifolates claim." Appx34. The court thus

determined that "[u]nder *Festo*, Lilly's narrowing amendment triggers a presumption of surrender that Lilly must rebut to sustain its doctrine of equivalents claim." *Id.* The court concluded, however, that the "tangential exception" to prosecution history estoppel applied—because Lilly's claims were "narrowed to overcome a rejection in view of Arsenyan, a prior art article about a different antifolate, methotrexate." Appx12-13; Appx37 (similar). The court understood Lilly to have "argue[d to the examiner] that the invention was new and nonobvious because it used the pretreatment regimen in combination with administration of pemetrexed disodium to treat the cancer and reduce the toxicities associated with pemetrexed disodium administration." Appx37. The court concluded that Lilly's "narrowing amendment (from antifolates as a class to pemetrexed disodium) was only tangential to the accused pemetrexed equivalent—pemetrexed ditromethamine." *Id.; see also* Appx13 ("Lilly's rationale for limiting its claim to pemetrexed disodium (to avoid a rejection based on the prior art Arsenyan) is tangential to the accused equivalent—pemetrexed ditromethamine.").

B. The District Court's Ruling That the Disclosure-Dedication Rule Does Not Bar Lilly From Relying on the Doctrine of Equivalents

Dr. Reddy's separately argued that because an ordinarily skilled artisan would read the '209 patent as disclosing but not claiming pemetrexed ditromethamine, Lilly had dedicated the latter to the public and could not assert its equivalence to pemetrexed disodium. Appx37-38; *see also* §I.B.1, *supra*.

In its summary judgment order, the district court gave two reasons for rejecting that argument: **(1)** "the '209 Patent did not expressly incorporate Akimoto by reference"; and **(2)** in the district court's view, "no POSA would understand Akimoto to specifically disclose pemetrexed, tromethamine, or pemetrexed ditromethamine from the broader genus of compounds that Akimoto discloses unless they knew to go looking for it." Appx38-39.

After trial, the court reached the same conclusion for similar reasons: "Because Akimoto was not expressly incorporated, as required, in the '209 Patent, and in any event Akimoto does not specifically disclose pemetrexed ditromethamine as an alternative to pemetrexed disodium, the disclosure-dedication rule does not bar Lilly's doctrine of equivalents

claim." Appx14. The court added that "the reference to Akimoto and what was contained therein amounts to a generic reference which does not dedicate all members of a particular genus to the public." *Id.*

C. The District Court's Ruling That Dr. Reddy's Infringes Under The Doctrine of Equivalents

After concluding that neither prosecution history estoppel nor disclosure-dedication barred Lilly from relying on the doctrine of equivalents, the district court concluded that Dr. Reddy's infringed under the doctrine of equivalents.

The court acknowledged that "the evidence shows that tromethamine differs from sodium with regards to the chemical properties alleged by Dr. Reddy's," and that "Lilly does not dispute that there are differences when the products are in solid form." Appx18. The court concluded, however, that the chemical differences between pemetrexed disodium and pemetrexed ditromethamine "with regards to solubility, stability, pH, and buffering capacity are irrelevant in the context of the claimed method including this Court's claim construction." *Id.* That was because, according to the court, the specification "explicitly identifies [the invention] as 'a method of reducing the toxicity associated

with the administration of an antifolate'"—even though none of the claims recite such a method. Appx16.

Based on its understanding of "the '209 Patent [as] claim[ing] [a] method of treatment," Appx19, the court found that an ordinarily skilled artisan would be someone "who works to mitigate the toxicities of chemotherapy" and "would focus on the pemetrexed treatment that the patient receives." Appx16. The court performed its equivalence analysis under the purportedly "relevant context that the claim relates to medical treatment," and determined that because "pemetrexed ditromethamine treats the patient's cancer in exactly the same way as pemetrexed disodium," the former is an equivalent of the latter. Appx17.

Because Dr. Reddy's does not provide care to patients, the district court found that Dr. Reddy's did not directly infringe. Dr. Reddy's also disputed indirect infringement, pointing to evidence "that it selected tromethamine, in good-faith belief, to avoid infringing the '209 Patent." Appx19-20. The district court did not dispute Dr. Reddy's good faith belief, but ruled that Dr. Reddy's "cannot avoid intent or infringement on the bases that it possessed a 'good faith belief that its proposed product[s] would not infringe.'" Appx21.

After trial, the district court entered final judgment that Dr. Reddy's NDA would infringe claims 9, 10, 12-15, 18, 19, 21, and 22 of the '209 patent, and ordered that the effective date of FDA approval be delayed until after that patent expires. Appx7-8; Appx1. Dr. Reddy's now appeals.

SUMMARY OF ARGUMENT

The district court's judgment relies on clear misapplications of legal limitations on the doctrine of equivalents. In prosecution, Eli Lilly tried to broadly claim methods of administering "antifolate[s]." An examiner's prior-art-based rejection directly presented Lilly with the choice of *how much* of the category of "antifolate[s]" to give up. In response, Lilly chose to give up *all* "antifolate[s]" except for the specific "pemetrexed disodium" compound in its commercial ALIMTA product. Lilly amended its claims to replace "antifolate" with "pemetrexed disodium" and stuck fastidiously to "pemetrexed disodium" claims through prosecution of three generations of patent applications. Years later, Lilly's competitors relied on that choice to develop and seek FDA approval for competing products with a different active ingredient (pemetrexed ditromethamine). The doctrine

of equivalents is fundamentally not an opportunity for patentees who regret these sorts of choices to rescind them. The Supreme Court has instructed that the doctrine is "premised on language's inability to capture the essence of innovation," and that the doctrine should only be applied when that premise holds, lest the doctrine defeat the important public notice functions of patent claims and prosecution history.

As explained below, the district court's judgment misapplied three legal principles that limit the scope of that doctrine: **(1)** the "tangential" exception to prosecution history estoppel, **(2)** the disclosure-dedication rule, and **(3)** the requirement that the equivalence analysis remain tethered to specific claim language rather than the invention "as a whole." Had the district court properly applied any one of those principles, Lilly's infringement claims would have failed as a matter of law.

First, the district court erred as a matter of law in finding prosecution history estoppel did not apply, instead accepting Lilly's arguments for invoking the "tangential" exception. This Court has emphasized that the "tangential" exception is "very narrow," that patentees cannot avoid prosecution history estoppel by arguing that they surrendered more than they needed to in prosecution to avoid a piece of prior art, and that the

"tangential" exception does not apply when an alleged equivalent and the reason for an amendment both concern the same claim element. The district court's reasoning runs counter to all of those principles and threatens to expand the "tangential" exception beyond its proper scope. Proper application of prosecution history estoppel (and its narrow tangential exception) requires judgment for Dr. Reddy's.

Second, the district court erred as a matter of law by not applying the disclosure-dedication rule to bar Lilly's invocation of the doctrine of equivalents. In contrast to its overly broad view of the tangential exception, the district court took an unduly narrow view of the disclosure-dedication rule. Where, as here, a patent discloses but does not claim an alternative to what it does claim, the alternative is dedicated to the public. This Court has specifically held that the "disclosure" need not be *in haec verba* or to the degree necessary to comply with §112—it need only be apparent to a person of ordinary skill in the art. In direct contravention of that precedent, the district court explicitly required "incorporation by reference" and more specific disclosure than this Court requires even in the §112 context.

Third, the district court's equivalence analysis fundamentally ignores that Lilly's claims are directed to "methods for administering" drugs, not "methods for treating diseases." In *Warner-Jenkinson*, the Supreme Court held that the equivalence analysis must focus on specific claim language, rather than the invention "as a whole." In this case, the district court dismissed as categorically "irrelevant" differences between the accused and claimed methods, on the theory that what mattered were the broader "medical treatment" objectives of the claims and not the "methods for administering" actually claimed.

As a result of the district court's errors, Lilly secured a judgment enjoining Dr. Reddy's from marketing and selling a product that it was reasonably entitled to believe Lilly had disclaimed several times over. Any one of the district court's three errors is reason enough to reverse. An affirmance here would set a dangerous precedent for the patent system: It would allow patent owners to *intentionally* narrow claims to avoid prior art, and then broadly expand the reach of their claims through litigation to cover matters they could have tried, *but chose not*, to claim—after the public has relied on their choice.

STANDARD OF REVIEW

"Whether prosecution history estoppel applies to a particular argument, and thus whether the doctrine of equivalents is available for a particular claim limitation, is a question of law reviewed de novo." *EMD Millipore Corp. v. Allpure Techs., Inc.*, 768 F.3d 1196, 1201 (Fed. Cir. 2014); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1312 (Fed. Cir 2006).

The "disclosure-dedication rule likewise presents a question of law, subject to de novo review." *Toro Co. v. White Consol. Indus. Inc.*, 383 F.3d 1326, 1331 (Fed. Cir. 2004).

"[I]nfringement, whether literal or under the doctrine of equivalents, is a question of fact." *Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 1105 (Fed. Cir. 2000). Where the relevant facts are undisputed, and no reasonable factfinder could find equivalence, infringement under the doctrine of equivalents may be resolved as a matter of law. *Advanced Steel Recovery, LLC v. X-Body Equip., Inc.*, 808 F.3d 1313, 1319 (Fed. Cir. 2015) (citing *Warner-Jenkinson*, 520 U.S. at 39 n.8).

ARGUMENT

I. The District Court Erroneously Applied the "Tangential" Exception To Rule That Prosecution History Estoppel Does Not Bar Lilly From Relying on the Doctrine of Equivalents.

A. The "Tangential" Exception is a Narrow Exception to the Rule of Prosecution History Estoppel.

The general rule of prosecution history estoppel is that a patentee cannot surrender literal claim scope in prosecution to obtain its patent, then later use the doctrine of equivalents in litigation to recapture some or all of the surrendered scope. *Festo*, 344 F.3d at 1365. By narrowing claims to obtain a patent, the applicant "recognize[s] and emphasize[s] the difference between the" original and amended claims "and proclaim[s] his abandonment of all that is embraced in that difference." *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126, 136 (1942); *see also Festo*, 535 U.S. at 740 (narrowing "amendment may be presumed to be a general disclaimer of the territory between the original claim and the amended claim").

That rule is longstanding and necessary to preserve the public notice function of patent claims and prosecution history. *See, e.g.*, *Schriber-Schroth*, 311 U.S. at 220-21; *Exhibit Supply*, 315 U.S. at 136; *Smith v. Magic City Kennel Club*, 282 U.S. 784, 790 (1931); *Weber Elec.*

Co. v. E.H. Freeman Elec. Co., 256 U.S. 668, 677-78 (1921); *Morgan Envelope Co. v. Albany Perforated Wrapping Paper Co.*, 152 U.S. 425, 429 (1894); *Shepard v. Carrigan*, 116 U.S. 593, 598 (1886).

In *Festo*, the Supreme Court articulated three exceptions to the general rule. Where, as here, the patentee narrows a claim limitation for a reason related to patentability, "the court should presume that the patentee surrendered all subject matter between the broader and the narrower language." 535 U.S. at 740. The patentee then bears the burden to rebut that presumption, by showing that its narrowing amendment fits into one of three exceptions:

> **[1]** The equivalent may have been unforeseeable at the time of the application; **[2]** the rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question; or **[3]** there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question.

Id. at 740-41 (bracketed numbers added). *Festo* described those exceptions as "cases … where [an] amendment cannot reasonably be viewed as surrendering a particular equivalent," or in other words, where "one skilled in the art *could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent*." *Id.*

In this case, it is undisputed that the predicates for prosecution history estoppel apply—*i.e.*, that Lilly narrowed its claims for a substantial reason related to patentability and that Dr. Reddy's accused product falls within the presumptively surrendered territory between the earlier "antifolate[]" claims and the ultimately issued "pemetrexed disodium" claims. Appx34. Neither Lilly nor the district court invoked the first or third exceptions to prosecution history estoppel. Only the "tangential" exception is at issue.

Since the Supreme Court first announced the "tangential" exception in *Festo*, this Court has elaborated on the exception's scope and meaning. At least nineteen times in published decisions, this Court has rejected patentees' arguments relying on that exception, sometimes reversing district courts for accepting those arguments.[1] The small

[1] *Integrated Tech. Corp. v. Rudolph Techs., Inc.*, 734 F.3d 1352, 1358-59 (Fed. Cir. 2013) (reversing infringement judgment); *Energy Transp. Grp, Inc. v. William Demant Holding A/S*, 697 F.3d 1342, 1359 (Fed. Cir. 2012); *Felix v. Am. Honda Motor Co.*, 562 F.3d 1167, 1184 (Fed. Cir. 2009); *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1364-65 (Fed. Cir. 2008) (reversing infringement judgment); *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1217-18 (Fed. Cir. 2008); *Int'l Rectifier Corp. v. IXYS Corp.*, 515 F.3d 1353, 1359 (Fed. Cir. 2008); *Honeywell Int'l Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1315-16 (Fed. Cir. 2008); *Schwarz Pharma, Inc. v. Paddock Labs., Inc.*, 504 F.3d 1371, 1377-78 (Fed. Cir. 2007); *Cross Med. Prods., Inc. v. Medtronic*

handful of published decisions where a patentee successfully relied on the "tangential" exception present unique circumstances and further underscore the narrowness of that exception.[2]

This Court has emphasized that the tangential exception is "'very narrow.'" *Integrated Tech.*, 734 F.3d at 1358 (quoting *Cross Med.*, 480 F.3d at 1342); *Honeywell*, 523 F.3d at 1315 (same). The relevant question is "whether *the reason* for the narrowing amendment was peripheral, or not directly relevant, to the alleged equivalent." *Festo*, 344 F.3d at 1369. The patentee must show that there *was* an actual reason for the

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Sofamor Danek, Inc., 480 F.3d 1335, 1341-43 (Fed. Cir. 2007) (reversing infringement judgment); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1313-16 (Fed. Cir. 2006) (reversing infringement judgment); *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1383 (Fed. Cir. 2005); *Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1306 (Fed. Cir. 2005); *Research Plastics, Inc. v. Fed. Packaging Corp.*, 421 F.3d 1290, 1298-99 (Fed. Cir. 2005); *Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1384-86 (Fed. Cir. 2005); *Bus. Objects, S.A. v. Microstrategy, Inc.*, 393 F.3d 1366, 1374 (Fed. Cir. 2005); *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1357 (Fed. Cir. 2004); *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 347 F.3d 1355, 1360 (Fed. Cir. 2003); *Festo*, 344 F.3d at 1371-73 (en banc); *Pioneer Magnetics, Inc. v. Micro Linear Corp.*, 330 F.3d 1352, 1357 (Fed. Cir. 2003).

[2] *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1290-92 (Fed. Cir. 2010); *Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1369-70 (Fed. Cir. 2010); *Regents of Univ. of Cal. v. Dakocytomation Cal. Inc.*, 517 F.3d 1364, 1377-79 (Fed. Cir. 2008); *Primos, Inc. v. Hunter's Specialties, Inc.*, 451 F.3d 841, 848-49 (Fed. Cir. 2006); *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 385 F.3d 1360, 1367-71 (Fed. Cir. 2004).

amendment that is "objectively apparent" and "discernible from the prosecution history record." *Id.* at 1368-69; *see also Felix*, 562 F.3d at 1184; *Biagro*, 423 F.3d at 1306.

B. The District Court Misapprehended and Misapplied *Festo*'s Tangential Exception.

In this case, the district court erred by accepting Lilly's argument that the narrowing amendment from "antifolate" to "pemetrexed disodium" was tangential to the accused equivalent (pemetrexed ditromethamine), on the theory that Lilly surrendered more than it needed to distinguish the cited Arsenyan prior art. Appx12-13; Appx37. The court emphasized that Lilly's change from "antifolate" to "pemetrexed disodium" was "to overcome a rejection in view of Arsenyan, a prior art article *about a different antifolate*, methotrexate." Appx12-13; *see also id.* ("Lilly's rationale for limiting its claim to pemetrexed disodium (to avoid a rejection based on the prior art Arsenyan) is tangential to the accused equivalent—pemetrexed ditromethamine."); Appx37. However, the amendment deliberately narrowed from all antifolates to one specific antifolate, giving up all others—including pemetrexed ditromethamine—to overcome the rejection based on "antifolate[s]."

The district court's reasoning is directly contrary to two clear principles this Court's post-*Festo* precedents have established concerning the "tangential" exception. First, patentees cannot avoid the consequences of narrowing amendments in prosecution by arguing that they surrendered more than they needed to overcome a prior art rejection. What matters is what was actually surrendered. Second, when the alleged equivalent and the rejection prompting an amendment both concern the same claim element, the tangential exception cannot apply. The district court's reasoning is also contrary to the fundamental public notice principles emphasized by the Supreme Court. And it is not supported by the handful of cases in which this Court has accepted tangential-exception arguments. An affirmance in this case would vastly expand the "tangential" exception and threaten to swallow the general rule of prosecution history estoppel.

1. Narrowing Amendments Are Read for What They Actually Surrender, Not Just What Was Necessary to Surrender to Overcome a Rejection.

In *Festo*, on remand from the Supreme Court, this Court declined to try to "anticipate the instances of mere tangentialness that may arise."

344 F.3d at 1369. From the ensuing decade-and-a-half of precedent, however, clear guideposts emerge.

Among the clearest is that narrowing amendments are *not* treated as if the patentee surrendered only what it needed to overcome the examiner's rejection. Consistent with the public-notice function of claims and prosecution history, what matters is what the patentee *actually surrendered*, not what the patentee strictly *needed* to surrender, or what the patentee might wish in hindsight that it had not surrendered. *Integrated Tech.*, 734 F.3d at 1358; *Lucent*, 525 F.3d at 1218; *Int'l Rectifier*, 515 F.3d at 1359; *Schwarz*, 504 F.3d at 1377-78. In other words, the tangential exception is not a patentee's-buyer's-remorse exception.

This Court's decision in *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356 (Fed. Cir. 2005) makes the point especially clearly:

> Because the sole purpose of the amendment was to avoid the effect of the Iwamoto reference, Norian argues, the prosecution history should not be interpreted as disclaiming pure solutions that are made from more than a single solute.
>
> The problem with that argument is that *there is no principle of patent law that the scope of a surrender of subject matter during prosecution is limited to what is absolutely necessary to avoid a prior art reference that was the basis for an examiner's rejection.* To the contrary, it frequently happens

> that patentees surrender more through amendment than may have been absolutely necessary to avoid particular prior art. In such cases, [the Court] has held the patentees to the scope of what they ultimately claim, and [has] not allowed them to assert that claims should be interpreted as if they had surrendered only what they had to.

Id. at 1361-63.[3] This Court has confirmed that principle repeatedly in the context of the tangential exception. The Court has consistently rejected arguments by patentees like Lilly that the tangential exception should apply when an alleged equivalent falls within the scope of subject matter that the patentee surrendered to avoid prior art, but did not necessarily need to surrender. *E.g.*, *Lucent*, 525 F.3d at 1218 ("[i]t is not relevant to the determination of the scope of the surrender that the applicant did not need to amend the claims" as much as it did "to overcome the prior art."); *Int'l Rectifier*, 515 F.3d at 1359 (applicant's "decision to

[3] The quoted passage directly addresses prosecution history disclaimer, 432 F.3d at 1361-62. *Norian* went on, however, to reject the patentee's arguments against prosecution history estoppel for similar reasons, holding that because "the district court was correct in [its] characterization of the prosecution history" regarding disclaimer, it followed that "Norian is not entitled to prevail on a doctrine of equivalents theory." *Id.* at 1363. "[T]he prosecution disclaimer standard 'is the same standard applicable, in the context of doctrine of equivalents, to the doctrine of argument-based estoppel." *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1363 (Fed. Cir. 2003) (quoting *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1326 (Fed. Cir. 2003)).

claim [a] structure using [a] limiting term … whether or not *required* to overcome the [examiner's] rejection, cannot be described as only tangential[]") (original emphasis); *Schwarz*, 504 F.3d at 1377 ("The fact that the inventors may have thought after the fact that they could have relied on other distinctions in order to defend their claims is irrelevant and speculative"); *cf. Chimie*, 402 F.3d at 1383 ("'[A]n amendment made to avoid prior art that contains the equivalent in question is not tangential. It does not follow, however, that equivalents not within the prior art must be tangential to the amendment.'") (citation omitted).

Integrated Technology closely parallels this case. There, the patentee initially claimed a system for capturing images regardless of whether a "probe tip" was or was not in contact with a "viewing window." 734 F.3d at 1356. In response to a rejection, the patentee narrowed the claim to require contact. *Id.* at 1357-58. The patentee argued that the amendment was tangential to the asserted equivalent because it "did not distinguish the prior art based on the invention requiring physical contact between the probe tip and viewing window." *Id.* The Court rejected that argument. Even if the patentee "*did not need* to surrender a lack of physical contact between the probe tip and window in either

state to overcome" the prior art, "*[t]he dispositive fact is that [it] chose to do so*." *Id.* at 1358. So too here. As in *Integrated Technology*, Lilly's "representations convey to the public that it was relying on [the amended term] to overcome the prior art. The public is entitled to rely on those representations." *Id.* at 1359.

The district court's reasoning in this case is directly contrary to the principle articulated in *Norian* and applied in *Integrated Technology*, *Lucent*, *International Rectifier*, and *Schwarz*. It is true that Arsenyan is "a prior art article about a different antifolate, methotrexate." Appx12. And it is also true that Lilly argued that its invention was new "because it used the pretreatment regimen in combination with administration of pemetrexed disodium …" Appx37. But it does not follow that Lilly's rationale for amending its claims from "an antifolate" to "pemetrexed disodium" is somehow "tangential" to Dr. Reddy's pemetrexed ditromethamine. Lilly began with claims to all "antifolate[s]." When confronted with a prior art reference relating to one "antifolate," Lilly did not narrow its claims to *some* antifolates—e.g., to "pyrrolopyrimidine derivative antifolates," or "pemetrexed and its salts." *See Statement of the Case* §I.B.2.b*, supra*. It deliberately and specifically narrowed its

claims to one antifolate—"pemetrexed disodium," clearly giving up *all other antifolates*. And it repeatedly emphasized in its remarks to the examiner that the amended claims to "pemetrexed disodium" differed from the prior art the examiner cited, discussing how the prior art "does not disclose *pemetrexed disodium*" nor the "use of vitamin B12 or a pharmaceutical derivative to reduce the toxicity associated with the administration of *pemetrexed disodium*." *See* Appx6379-6383. Tellingly, Lilly did not say "pemetrexed salts" or even "pemetrexed," instead repeatedly referring to the efficacy, side effects, or toxicity associated with "*pemetrexed disodium*." *Id.* Yet, when it wanted to speak in generalities, Lilly knew how to do so, referring to "methylmalonic acid lowering agents" as well as vitamin B12. Appx6382.

It is no answer to say, as Lilly did below, that Lilly's amendments from "an antifolate" to "pemetrexed disodium" "were about the active antifolate compound," as opposed to "different salt forms of pemetrexed." Appx1921. That is inconsistent with Lilly's narrowing amendment and arguments during prosecution, which singled out, discussed, and claimed only "*pemetrexed disodium*." Pemetrexed ditromethamine is not tangential to what Lilly gave up—it is directly within the path of

narrowing from all antifolates to one specific antifolate, a decision made to overcome the examiner's rejection of claims to "antifolate[s]." That the pemetrexed ion in a pemetrexed salt antagonizes folic-acid-dependent processes in the human body is a general principle of pharmacology, not anything Lilly discovered or was unaware of. Appx4460-4461(148:20-149:11).

Lilly knew how to discuss "different salt forms of pemetrexed" when it wanted to. Tellingly, Lilly had other patents and applications where it claimed or tried to claim "[p]emetrexed" while defining that term as including "the stable salts, acids, and free base forms thereof." Appx7977(3:10-20); Appx7978(5:19-33); *see also* Appx1506; Appx1515-1517 (efforts to obtain similar coverage in Europe); Appx6307-6333 (ALIMTA label, describing the active ingredient as either "pemetrexed" or "pemetrexed disodium"); Appx6404-6425, Appx6426-6430 (Lilly-licensed Taylor and Akimoto patents, describing broader classes of antifolates that included pemetrexed salts but not methotrexate). Thus, had Lilly wanted to claim all therapeutically effective forms of pemetrexed, it could have tried to do so by amending "an antifolate" to, for example, "pemetrexed salts," or just "pemetrexed"—not referring to

any particular salt form. But in the '209 patent Lilly chose to claim "pemetrexed disodium." The public is entitled to rely on that choice. Lilly's apparent remorse at having surrendered as much as it did is no reason to rewrite the '209 patent's prosecution history.

Nor is there any merit to Lilly's argument below that *Schwarz*, *Biagro* and other cases "might be more pertinent were Lilly trying to claim a scope of equivalents with respect to a different antifolate such as lometrexol …." Appx423. *Lilly* ultimately bore the burden of explaining why it chose to narrow to "pemetrexed disodium" and not "pemetrexed," or some other broader term. *See Festo*, 535 U.S. at 740 (where patentee "is unable to explain the reason for [its] amendment" with respect to a claim element, "estoppel not only applies but also 'bar[s] the application of the doctrine of equivalents as to that element'") (quoting *Warner-Jenkinson*, 520 U.S. at 33). Lilly offered no such explanation. *E.g.*, Appx8150-8152; Appx8355.

As Lilly would have it, a court should treat Lilly's claims to "pemetrexed disodium" as if they were *original* claims entitled to a full range of equivalents, rather than *amended* claims that were deliberately narrowed to that precise compound from "antifolate[s]" generally. The

point of prosecution history estoppel is that narrowing amendments limit the patentee's ability to rely on the doctrine of equivalents. *Schriber-Schroth*, 311 U.S. at 221; *Festo Corp.*, 535 U.S. at 733. Lilly's argument would make prosecution history estoppel all but meaningless.

To the extent Lilly would ask the Court to analyze "pemetrexed" and "disodium" separately (thus splitting the actual compound Lilly claimed into two), that would not help Lilly, as it would leave no explanation at all for Lilly's choice to narrow its claims to the "disodium" salt of pemetrexed. Again, where a patentee is "unable to explain the reason" for such a narrowing amendment in terms objectively apparent from the prosecution record, the patentee cannot avoid prosecution history estoppel. *Festo*, 535 U.S. at 740; *Festo*, 344 F.3d at 1368-69; *Felix*, 562 F.3d at 1184; *Biagro*, 423 F.3d at 1306.

At bottom, this is not a case where Lilly "lacked the words to describe" the equivalent during prosecution, or where Lilly's amendment "cannot reasonably be viewed as surrendering a particular equivalent." *Festo*, 535 U.S. at 734, 740. Lilly was well aware that pemetrexed, like other active moieties, had multiple salts. Had Lilly wanted to disclaim Arsenyan's methotrexate while still preserving claims to antifolates

other than just pemetrexed disodium, the words were readily available—as demonstrated by Lilly's other patents and patent applications, as well as its own product label. *See supra* pp. 44-45.

Instead of choosing any broader intermediate set of compounds, Lilly clearly and specifically chose to limit its claims to "pemetrexed disodium," the specific salt compound in its commercial product. In hindsight, Lilly may regret that it surrendered more than it needed to distinguish the prior art, but that is legally irrelevant. *Integrated Tech.*, 734 F.3d at 1357-58; *Lucent*, 525 F.3d at 1218; *Int'l Rectifier*, 515 F.3d at 1359; *Schwarz*, 504 F.3d at 1377-78. The district court's reliance on Lilly having surrendered more than it needed to surrender is wrong as a matter of law and reason enough to reverse.

2. The Tangential Exception Does Not Apply Where the Reason For the Amendment And the Equivalent in Question Both Concern the Same Claim Element.

Another clear guidepost in this Court's post-*Festo* precedents is that, where the reason for the amendment and the equivalent in question both relate to the same claim element, the tangential exception does not apply. *See, e.g.*, *Honeywell*, 523 F.3d at 1316 ("Because the alleged equivalent focuses on the IGV limitation, the amendment bore a direct,

not merely tangential, relation to the equivalent."); *Biagro*, 423 F.3d at 1306 ("Because both the reason for the amendment and the asserted equivalent relate to the concentration of the fertilizer, we affirm the trial court's conclusion that Biagro has not shown that the rationale underlying the amendment was merely tangential to the accused equivalent.").

That rule is consistent with the "narrow[ness]" of the tangential exception, *Integrated Tech.*, 734 F.3d at 1358 (quoting *Cross Medical*, 480 F.3d at 1342); *Honeywell*, 523 F.3d at 1315 (same), and with the Supreme Court's explanation of prosecution history estoppel in *Festo*. If a patent application once encompassed a purported equivalent, and then the applicant surrendered that equivalent in response to a rejection, "prosecution history has established that the inventor turned his attention to the subject matter in question, knew the words for both the broader and narrower claim, and affirmatively chose the latter." 535 U.S. at 734-35. Where, as here, the examiner's rejection and the subsequent amendment show that the inventor "turned his attention" to a specific claim element, an alleged equivalent of that same element cannot

reasonably be said to be "tangential" to the rationale for the amendment. *See Honeywell*, 523 F.3d at 1316; *Biagro*, 423 F.3d at 1306.

The Supreme Court described the "tangential" exception as a case "where the amendment cannot reasonably be viewed as surrendering a particular equivalent." *Festo*, 535 U.S. at 740. But here, the examiner's rejection focused Lilly's attention on the "antifolate" limitation and presented it with a choice of how far to go in distinguishing prior art. Lilly deliberately chose to give Arsenyan a wide berth, limiting its claims to "pemetrexed disodium." The public and Lilly's competitors are entitled to rely on that choice. *Planet Bingo, LLC v. GameTech Int'l, Inc.*, 472 F.3d 1338, 1344 (Fed. Cir. 2006).

As the district court found and as Lilly did not dispute, Lilly's amendment narrowing "antifolate" to "pemetrexed disodium" was in direct response to the examiner's prior art rejections, which focused on that limitation. Appx34. Contrary to *Honeywell* and *Biagro*, the district court nonetheless held that an alleged equivalent to that narrowed element (pemetrexed ditromethamine) is "tangential" to the rationale for that amendment.

3. The District Court's Reasoning Dramatically Expands the Tangential Exception, Threatening the General Rule.

The district court relied on *Regents of University of California v. Dakocyomation California Inc.* to support its result, Appx35-36, but its reliance on that case is misplaced. Instead, the district court's approach grossly expands the scope of the tangential exception.

Regents is one of very few instances where this Court has found that a particular case's facts fit the "very narrow" tangential exception. The patent-in-suit claimed methods of labeling targeted regions of chromosomal DNA using nucleic acid probes, which bonded to the target regions. 517 F.3d at 1369. Compared to prior-art methods, the claimed methods achieved more specific labeling by preventing probes from binding to "repetitive" (i.e., non-target) sequences. *Id.* The specification described three techniques for disabling probes from bonding to repetitive sequences—"blocking, selective removal, and screening"—and the claims initially encompassed methods employing any of those techniques. *Id.* at 1369, 1377-78. To overcome an examiner's rejection over prior art that taught variants of those three techniques, the patentee amended its claims to require use of a "blocking nucleic acid." *Id.* at 1377-

78. At trial, the parties agreed that the "blocking nucleic acid" in the claims must be DNA or RNA, whereas the accused product used blocking nucleic acids made of PNA. *Id.* at 1376.

A divided panel of this Court concluded that prosecution history estoppel did not apply because the "'nucleic acid' limitation was never narrowed during prosecution and was not at issue in the office action rejecting the claims … or the patentees' remarks accompanying the amendment." *Id.* at 1378. Instead, "the focus of the patentees' arguments centered on the method of blocking—not on the particular type of nucleic acid that could be used for blocking." *Id.* Where, as in *Regents*, a patentee narrows one aspect of a claim limitation in response to an examiner's rejection concerning that aspect, but never narrowed a second aspect of the limitation, then the patentee's later assertion of infringement by equivalents with respect to the second aspect can be fairly characterized as "tangential."

Regents is nothing like this case. Unlike "nucleic acid" in *Regents* (a term that appeared in the claims both before and after amendment), no part of replacing "antifolate" with "pemetrexed disodium" during prosecution can be characterized as doing anything but "narrow[ing]" the

relevant term. *Id.* at 1378. The relevant limitation that was narrowed is, and was, the "antifolate" term, which Lilly specifically narrowed from "antifolate" generally to only "pemetrexed disodium." The breadth of the original "antifolate" term in Lilly's original claims figured explicitly in the examiner's rejection, and in response Lilly narrowed that term to recite only one antifolate: *pemetrexed disodium*. Indeed, Lilly consistently and repeatedly emphasized *pemetrexed disodium* in its remarks to the examiner—relying on "*pemetrexed disodium*" to obtain allowance. *See supra Statement of the Case* §I.B.2.b. Unlike in *Regents*, there is no second aspect of "antifolate" (or "pemetrexed disodium") that "was not at issue in the office action rejecting the claims … or the patentees' remarks accompanying the amendment." *Regents*, 517 F.3d at 1378. *Regents* does not support the district court's result here.

Insituform resembles *Regents* and only underscores the contrast with this case. In *Insituform*, the patent claimed a method of impregnating an absorbent layer with resin, which involved using a vacuum to draw resin into the layer. 385 F.3d at 1364. To overcome a rejection based on prior art that taught to apply the vacuum at a location distant from where the resin was introduced, the patentee incorporated

the limitations from four dependent claims into a single independent claim. *Id.* at 1369. In so doing, the patentee narrowed its claims to require application of the vacuum nearer to the resin's introduction. *Id.* at 1368-69. The patentee also, and for reasons unrelated to the rejection, happened to narrow its claims to require use of a single vacuum cup, as opposed to multiple cups (which the original claim permitted). *Id.* at 1370-71. This Court concluded that the tangential exception applied only to the latter, single-cup amendment, which was not swept along with the vacuum-source amendment into the rule of prosecution history estoppel. *Id.*

In this case, unlike *Regents* and *Insituform* (but like *Honeywell* and *Biagro*), there is no question that Lilly narrowed the "antifolate" term to "pemetrexed disodium" to overcome the examiner's prior art rejection. If anything, Lilly's other contemporaneous amendments only reinforced that Lilly had decided to surrender coverage of all "antifolate[s]" and retain only "pemetrexed disodium." As noted above, Lilly changed the title of its patent from "Novel *Antifolate* Combination Therapies" to "*Vitamin B12 and Pemetrexed Disodium* Combination Therapies."

Statement of the Case §I.B.2.b, *supra*.[4] To apply the "tangential" exception to Lilly's amendment and allow Lilly to walk back the deliberate choice it made in prosecution would grossly expand that "very narrow" exception, in contravention of a decade and a half of this Court's precedent applying that exception, and more than a century of Supreme Court precedent on prosecution history estoppel. As between holding Lilly to the consequences of its choice and punishing the public and Lilly's

[4] The few other precedential decisions where a "tangential exception" argument succeeded also do not help Lilly. *Primos* nominally referred to the "tangential" exception, but the substance of the Court's reasoning indicates that prosecution history estoppel did not apply at all because the accused device did not fall within the territory literally surrendered by the amendment. 451 F.3d at 849. In *Funai*, the Court concluded that an amendment requiring that a component be made of "an insulating material" did not foreclose equivalents arguments with respect to the specific "nature of the insulating material," which "was not at issue during prosecution." 616 F.3d at 1369. And in *Intervet*, the Court reasoned in likely dicta that although an amendment narrowing the scope of claimed DNA sequences to a specific porcine type ("PCV-2") barred assertion of non-porcine sequences as equivalents, it did not further foreclose an argument that porcine sequences "with over 99%" similarity to PCV-2 could be equivalent to that strain. 617 F.3d at 1290 n.5, 1292. By contrast, pemetrexed ditromethamine concededly falls within the territory surrendered by Lilly's amendment of "an antifolate" to "pemetrexed disodium," the antifolate limitation was specifically at issue during prosecution, and pemetrexed ditromethamine is undisputedly *not* pemetrexed disodium.

competitors for relying on that choice, precedent requires the former. The district court's contrary decision must be reversed.

II. The District Court Erroneously Ruled That the Disclosure-Dedication Rule Does Not Bar Lilly From Relying on the Doctrine of Equivalents.

After relying on an erroneously expansive conception of the "tangential" exception to prosecution history estoppel, the district court relied on an erroneously narrow conception of the disclosure-dedication rule. Once again, the district court failed to enforce a fundamental legal limit on the doctrine of equivalents, to Lilly's benefit and to the detriment of the public and the patent system. That is an independent reason for reversal.

A. Lilly Disclosed, But Did Not Claim, Methods for Administering Pemetrexed Ditromethamine.

Under the disclosure-dedication rule, "when a patent drafter discloses but declines to claim subject matter … this action dedicates that unclaimed subject matter to the public." *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002) (en banc). Patentees "cannot assert the doctrine of equivalents to cover the disclosed but unclaimed" subject matter. *Id.* at 1055.

As this Court has explained, that limit on the doctrine of equivalents stems from similar public-notice principles as prosecution history estoppel. Patentees cannot use the doctrine of equivalents in litigation to recapture subject matter that the public was fairly entitled to assume the patentee relinquished. *Id.* at 1054-55. Thus, the disclosure-dedication rule "avoid[s] the problem of extending the coverage of an exclusive right to encompass more than that properly examined by the PTO." *Id.* at 1055 (citing *Keystone Bridge Co. v. Phoenix Iron Co.*, 95 U.S. 274, 278 (1877)). And by preventing "recapture [of] subject matter deliberately left unclaimed," courts give appropriate respect to "'the primacy of the claims in defining the scope of the patentee's exclusive right.'" *Id.* at 1054.

A paradigmatic example of disclosure and dedication is this Court's en banc decision in *Johnson*. The written description of the patent-in-suit stated that "'While aluminum is currently the preferred material for the substrate, other metals, such as stainless steel or nickel alloys may be used." 285 F.3d at 1055. The claims, however, recited only "a sheet of aluminum" and "the aluminum sheet." *Id.* Thus, this Court held that "[h]aving disclosed without claiming *the steel substrates*, Johnston cannot

now invoke the doctrine of equivalents to extend its aluminum limitation to encompass steel." *Id.*

This Court's precedent makes clear, however, that the disclosure-dedication rule is not narrowly limited to the circumstance in *Johnson* of a specification explicitly referring to an unclaimed equivalent as an alternative. The rule is broader, and merely requires a court to "determine from the specification's disclosure whether 'one of ordinary skill would have come to the conclusion that the inventor[] ha[s] identified [the unclaimed embodiment] as an alternative to [the claimed embodiment].'" *CSP Techs., Inc. v. Sud-Chemie AG*, 643 F. App'x 953, 959 (Fed. Cir. 2016) (discussing *Pfizer, Inc. v. Teva Pharms USA, Inc.*, 429 F.3d 1364, 1379 (Fed. Cir. 2005) and *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1366-67 (Fed. Cir. 2012)).

Thus, "the disclosure-dedication rule does not impose a § 112 requirement on the disclosed but unclaimed subject matter." *Toro*, 383 F.3d at 1334. "[D]isclosures implicating the disclosure-dedication rule need not directly relate to the description of the claimed invention," and need not appear in specific sections of the patent. *Id.* Indeed, the relevant "disclosure" may appear in references external to the patent, such

as a priority application or a referenced piece of prior art. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1297 (Fed. Cir. 2009) (priority application); *CSP Techs.*, 643 F. App'x at 958 ("later-filed continuation application based on the application that led to the patent in suit reinforce[d]" the disclosure-dedication determination). Finally, the patentee need not "specifically stat[e] that an [alleged equivalent] is an 'alternative,'" *CSP*, 643 F. App'x at 959, "expressly disclaim or disavow" the alleged equivalent, *Toro*, 383 F.3d at 1331, nor actually "intend" to dedicate the equivalent to the public, *id.* at 1332-33—all that is required is disclosure of the alleged equivalent, and failure to claim it.

In this case, the undisputed record amply meets that standard. A person of skill in the art would conclude that the inventor identified pemetrexed ditromethamine as an alternative to pemetrexed disodium. The inventor's decision not to actually claim pemetrexed ditromethamine means that that subject matter is dedicated to the public.

As discussed above, Lilly initially drafted its application to broadly claim methods of administering any "antifolate" drug. *See Statement of the Case* §I.B.1, *supra*. Like the patentee in *Johnson*, Lilly's patent's

specification refers to the subject matter it actually claimed as "preferred," while also identifying acceptable alternatives. Indeed, more than that, it identifies "pemetrexed disodium" as the "most preferred" antifolate and singles out other antifolates as "preferred examples":

> *Preferred examples of antifolates* include Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; *derivatives described by Akimoto in U.S. Pat. No. 4,997,838*; thymidylate synthase inhibitors as found in EPO application 239,362; and *most preferred*, Pemetrexed Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

Appx49(4:34-43). As also discussed above, at least six of the listed "preferred examples of antifolates" disclose "substituted ammonium salts," including the referenced "derivatives described in Akimoto" (the patent Lilly licensed). *Statement of the Case* §I.B.1, *supra*.

As Lilly's expert conceded, Akimoto discloses pemetrexed. Appx4561(249:4-13). And in unrebutted testimony, Dr. Reddy's expert explained that, as in Akimoto, chemical structures "are very commonly represented as frameworks or scaffolds with variables," and walked through the "very straightforward process" that a skilled artisan with the

'209 patent in hand would follow in "quickly" ascertaining that Akimoto taught pemetrexed. Appx4632-4635(320:25-323:22).

As to the ditromethamine salt of pemetrexed, Akimoto explicitly singles out "substituted ammonium" salts as "exemplif[ying] the salts of pharmaceutically acceptable bases" that can form from pemetrexed. Appx6438(14:41-47). That includes pemetrexed ditromethamine. No further disclosure is necessary to direct a person of skill in the art to pemetrexed ditromethamine. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art"). As the record showed, the group of "pharmaceutically acceptable" "substituted ammonium bases" is limited to only a handful of compounds. *See, e.g.,* Appx6339 (Table 7) (From 1982 to 2006, tromethamine was one of only three cations used in injectable drugs.). There was, thus, a reason a skilled artisan would readily recognize pemetrexed ditromethamine from that disclosure.

In 2000, tromethamine in particular was one of a handful of substituted ammonium bases that were FDA-approved. Appx6590 (*Remington*); Appx4635-4636(323:23-324:17). It is undisputed that by 2001, tromethamine was a common substituted-ammonium salt used in injectable

drugs. *See* Appx4474(162:15-17); Appx4613(301:13-14); Appx4637(325:8-25). Indeed, from 1982 to 2006, tromethamine was one of only three cations used in injectable dosage forms. Appx6339 (Table 7). And tromethamine remained a common cation for injectable pharmaceutical drugs as late as 2012. Appx6351 (Table 5). Moreover, a standard pharmacology textbook, *Remington: The Science and Practice of Pharmacy*, specifically identified two "[a]lternative salts that have proven useful in hygroscopicity" issues caused by sodium (as found in pemetrexed disodium): "hydrogen sulfate and tromethamine." Appx6590.

Thus, as a matter of law, the '209 patent's disclosure of "preferred examples of antifolates" that Lilly did not ultimately claim discloses the administration of pemetrexed ditromethamine, and dedicates it to the public. The district court's contrary reasoning rests on an erroneously narrow conception of the disclosure-dedication rule, and effectively "impose[s] a § 112 requirement on the disclosed but unclaimed subject matter," contrary to precedent. *Toro*, 383 F.3d at 1334.

B. The District Court's Decision Not to Apply the Disclosure-Dedication Rule Rests on Legal Errors.

As discussed above, *Statement of the Case §II.B.2*, the district court gave three reasons for refusing to apply the disclosure-dedication rule.

Each one is legally erroneous. The Court **(1)** required the '209 patent to incorporate Akimoto by reference, **(2)** required "specific" disclosure of pemetrexed ditromethamine as an "alternative" to pemetrexed disodium, and **(3)** stated that Akimoto was a "generic reference which does not dedicate all members of a particular genus to the public." Appx37-39; Appx13-14.

1. The Court Erroneously Required Incorporation By Reference.

The district court first erred to the extent it concluded Akimoto was irrelevant to the disclosure-dedication analysis simply because the '209 patent does not say it incorporates Akimoto by reference. According to the district court, "[b]ecause Akimoto was not expressly incorporated, *as required*, in the '209 patent … the disclosure-dedication rule does not bar Lilly's doctrine of equivalents claim." Appx14. There is no such rule.

This Court has never held that a source cited in a patent must be "incorporated by reference" for the disclosure-dedication rule to apply. "Incorporation by reference" is principally relevant to determining a patent's compliance with §112 or establishing a patent's priority date or availability as a prior art reference. *See, e.g.*, *Hollmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012) (priority); *Quaker City Gear Works, Inc. v.*

Skil Corp., 747 F.2d 1446, 1453-54 (Fed. Cir. 1984) (enablement); *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010). Here there is no question of Lilly trying to establish priority through Akimoto or anything similar. This Court has specifically held that the disclosure-dedication rule does *not* "impose a § 112 requirement on the disclosed but unclaimed subject matter," *Toro*, 383 F.3d at 1334.

As described above, the '209 patent amply satisfies the correct legal standard of disclosing to a person of ordinary skill in the art that pemetrexed ditromethamine may be an alternative to pemetrexed disodium. The '209 patent describes Akimoto as disclosing "[p]referred examples" of antifolates as alternatives to the "most preferred" antifolate, pemetrexed disodium. Appx49(4:42-43); *id.* (claims). Akimoto, in turn, discloses pemetrexed and its pharmaceutically acceptable substituted ammonium salts. *See* Appx6432-6433(1:4-3:17); Appx4561(249:4-15); Appx4632-4635(320:25-323:22). And within that category, trometham-ine was a known alternative to sodium and one of only a handful of known pharmaceutically acceptable substituted ammonium salts.

The district court cited *SanDisk* in support of its ruling, but *SanDisk* is inapposite. Appx13-14 (quoting *SanDisk*); Appx30 (same). In

SanDisk, the asserted patent expressly incorporated an earlier patent by reference. The Court considered whether the earlier, incorporated patent substantively identified the asserted equivalent as an alternative to embodiments claimed in the asserted patent. 695 F.3d at 1366-67. The asserted patent, however, did not describe the incorporated patent as disclosing any "preferred" embodiments. Instead, the asserted patent referred to the incorporated patent "only in general terms." *Id.* On those different facts, the Court in *SanDisk* concluded that the disclosure-dedication rule did not apply. *SanDisk* did not hold, however, that *only* patents or documents expressly incorporated by reference can be relevant in a disclosure-dedication rule analysis. Instead, it merely held that the evidence there was insufficient to "inform one of ordinary skill that the [in-that-case] incorporated document contains subject matter that is an alternative to a claim limitation." *Id.* at 1366; *CSP Techs.*, 643 F. App'x at 959 (discussing *SanDisk*, rejecting restrictive reading of that case). In this case, unlike in *SanDisk*, the '209 patent "sufficiently provide[s] notice to one of ordinary skill that [Akimoto] contains subject matter that is an alternative to the claimed" pemetrexed disodium as a matter of law.

695 F.3d at 1367. Neither *SanDisk* nor any other case supports the district court's erroneous reliance on an incorporation-by-reference standard.

2. The Court Erroneously Required *In Haec Verba* Disclosure of "Pemetrexed Ditromethamine" as an "Alternative" to Pemetrexed Disodium.

The district court's second reason for not applying the disclosure-dedication rule is similar to its first and likewise effectively imposes a §112-type requirement, which *Toro* rejected. The district court reasoned that because "Akimoto does not *specifically* disclose *pemetrexed ditromethamine* as an *alternative* to pemetrexed disodium, the disclosure-dedication rule does not bar Lilly's doctrine of equivalents claim." Appx14. But that is not the test—the test is what a person of ordinary skill in the art (with the '209 patent in hand) would reasonably conclude had been disclosed but not claimed.

Indeed, to require "specific" disclosure of "pemetrexed ditromethamine as an alternative," Appx14, in the context of the disclosure-dedication rule, is to require more than this Court does under the *actual* §112 requirement. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc) (written description

requirement "does not demand … that the specification recite the claimed invention *in haec verba*."). Moreover, this Court has specifically examined and rejected the argument that the disclosure-dedication rule requires "some language specifically stating that [the equivalent in question] is an 'alternative'" to the claimed embodiment. *CSP Techs.*, 643 F. App'x at 959. If such words were necessary, "an artful drafter could avoid describing embodiments as alternatives and make the patent immune to the disclosure-dedication doctrine." *Id.*

Rather than a requirement of form or particular words, "the requirement is one of substance where [a court] determine[s] from the specification's disclosure whether 'one of ordinary skill would have come to the conclusion that the inventor[] ha[s] identified [the unclaimed embodiment] as an alternative to [the claimed embodiment].'" *CSP Techs.*, 643 F. App'x at 959 (quoting *Pfizer*, 429 F.3d at 1379). The district court's heightened, formalistic requirement has no basis in precedent.

3. The Court's "Generic Disclosure" Reasoning Erroneously Disregards the Perspective of Persons of Ordinary Skill in the Art.

Finally, the district court's reference to Akimoto as a "generic reference which does not dedicate all members of a particular genus to

the public," Appx14, cannot withstand scrutiny. That reasoning misapprehends the record and fails to give legally required weight to the perspective of a person of ordinary skill in the art. *See* §II.A, *supra.*

The '209 patent itself focuses on pemetrexed disodium. The written description specifically refers to "pemetrexed disodium" as "most preferred," and to "derivatives described in Akimoto" as among the "[p]referred examples of antifolates." Appx49(4:34-43). The cross-reference to Akimoto is thus not a generic cross-reference to whatever chemicals Akimoto might happen to mention, but to "derivatives" related to the "most preferred" antifolate, pemetrexed disodium. A person of skill in the art would thus not need to "kn[o]w to go looking for it" independent of the specification to arrive at pemetrexed ditromethamine. Appx38-39. Instead, the '209 patent's specification points the skilled artisan to pemetrexed derivatives disclosed by Akimoto, which would include pemetrexed ditromethamine.

Lilly's expert conceded that Akimoto discloses pemetrexed. Appx4561(249:4-13). It is undisputable that Akimoto also explicitly singles out "substituted ammonium" salts as "exemplif[ying] the salts of pharmaceutically acceptable bases" that can form from pemetrexed.

Appx6438(14:41-47). And it was undisputed that the universe of "pharmaceutically acceptable" "substituted ammonium bases" was a small universe of compounds, and that tromethamine in particular was one of only a handful of substituted ammonium bases that were FDA-approved, and particularly suitable for injectable use. *See* §II.A, *supra*; Appx6590 (*Remington*); Appx4635-4636(323:23-324:17). Akimoto, viewed through the lens of a skilled artisan with the '209 patent in hand, plainly discloses pemetrexed ditromethamine.

Against the backdrop of that small genus of injectable, FDA-approved substituted ammonium bases, the '209 patent and Akimoto more than adequately disclosed pemetrexed ditromethamine as an alternative to the claimed disodium salt. In other contexts, this Court has considered arguments that a patent's disclosure of a "genus" is too broad and general to direct a person of skill in the art to species within the genus. This Court has recognized that "[v]erbatim disclosure of a particular species is not required" to direct a person of skill in the art to it if the genus is small, *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871-72 (Fed. Cir. 2015), or if a disclosure directs a person of skill in the art to "a much more limited class within" a broad disclosed

class. *Application of Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). This Court has concluded that a genus of dozens may direct persons of skill in the art to species within the genus as a matter of law. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-63 (Fed. Cir. 2007) (reversing district court, finding motivation to combine prior-art references to arrive at a specific pharmaceutical salt where "the genus of FDA-approved anions at the time was small, *i.e.*, only 53"). By any measure, Akimoto's disclosure of pemetrexed, coupled with the specific cross-reference from '209 patent, would be sufficient to disclose pemetrexed ditromethamine. That is particularly true since Akimoto further refers to a sufficiently "small" set of "*pharmaceutically acceptable*" "substituted ammonium bases."

At bottom, had the district court taken account of the perspective of a person of skill in the art, it would have recognized that a POSA would read Akimoto's list of pemetrexed salts against the backdrop of the '209 patent's specific preference for and exclusive claiming of pemetrexed disodium—not on a blank slate. Appx14; Appx38-39; §II.A, *supra*.

In light of the '209 patent's emphasis on using pemetrexed disodium as an anti-cancer drug and Akimoto's emphasis on "pharmaceutically acceptable bases," an ordinarily skilled artisan would have focused on

tromethamine as a known sodium substitute and one of the handful of "substituted ammonium" salts that had been approved by the FDA—and, as a matter of law, would have concluded that the '209 patent disclosed pemetrexed ditromethamine as an alternative. *See Pfizer*, 480 F.3d at 1362 (crediting testimony that "'part and parcel of pharmaceutically accepted[] was to look in pharmacopoeias and compendia' to find an anion having 'precedence for using within the pharmaceutical industry.'"); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1477, 1480 (Fed. Cir. 1997); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291-92 (Fed. Cir. 2013). Because Lilly's patent, and its cross-reference to Akimoto, discloses pemetrexed ditromethamine without claiming it, Lilly dedicated use of that antifolate to the public. The district court's infringement judgment should be reversed.

III. The District Court Erroneously Analyzed Infringement Of Claims to "Method[s] For Administering" Drugs As If They Were Claims to Methods For Treating Tumors.

Even if the Court concludes that Lilly was properly allowed to assert its theory of infringement under the doctrine of equivalents, the district court's analysis of equivalence erroneously disregarded key claim language. In *Warner-Jenkinson* and *Festo*, the Supreme Court

emphasized that the doctrine of equivalents should not "take[] on a life of its own, unbounded by the patent claims." *Warner-Jenkinson*, 520 U.S. at 28-29; *Festo*, 535 U.S. at 731 (similar). Thus, among other things, *Warner-Jenkinson* held that the doctrine should be applied "on an element-by-element basis," 520 U.S. at 40, focusing on specific claim language rather than "the invention as a whole." *Id.* at 29. This Court's precedent after *Warner-Jenkinson* has similarly emphasized that "the range of equivalents cannot be divorced from the scope of the claims." *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382 (Fed. Cir. 2000).

In this case, the claims are specifically drawn to "method[s] for administering pemetrexed disodium." As discussed above, "method for administering" is not an idle or accidental word choice. In prosecution, Lilly cancelled claims to "method[s] of inhibiting tumor growth." *Statement of the Case* §I.B.3, *supra*. The district court's equivalence analysis however, largely disregards that the claims are directed to "methods for administering" and analyzes equivalence as if Lilly had kept its claims for "method[s] of inhibiting tumor growth." Thus, the court emphasized that "[u]nder the relevant context that *the claim relates to*

medical treatment, pemetrexed ditromethamine *treats the patient's cancer* in exactly the same way as pemetrexed disodium." Appx17. In other words, the court relied on a comparison of what the two drugs do in the human body—*i.e.*, how they treat tumors *after* they have already been administered to the patient. *See, e.g.*, Appx17-18. And the court explicitly dismissed as "irrelevant" the differences in properties that are more relevant to *administering* the drugs in the first place, such as solubility, stability, pH, and buffering capacity. Appx18.

The district court's focus on "medical treatment," Appx17, is in some sense understandable. Many pharmaceutical patent claims recite either products or methods of treating diseases. And Lilly's patent is, of course, a pharmaceutical patent, and its claimed methods serve the ultimate *ends* of treating tumors while minimizing toxic side effects. Those considerations may have led the district court to emphasize its repeated view that the person of skill in the art is an "oncologist" rather than a "chemist." Appx15-17.

But under the district court's legally erroneous reasoning, *any* composition that treats cancer in a patient as pemetrexed disodium does would be an equivalent—perpetuating the exact abuse of the doctrine of

equivalents that *Warner-Jenkinson* admonished courts to prevent. The district court permitted its equivalence analysis to "take[] on a life of its own, unbounded by the patent claims." *Warner-Jenkinson*, 520 U.S. at 28-29. The *claims* here are directed to the *means* ("methods for administering" drugs) and not the ultimate *ends* (treating tumors or minimizing side effects). The '209 patent's written description discusses both the means and the ends, but the claims are directed to the means. An oncologist and a chemist might have different objectives or concerns with respect to administering cancer drugs. Even if it were fair to say, as the district court suggested, that an oncologist is more directly interested than a chemist in the ultimate ends of tumor-growth inhibition and toxic-side-effect reduction, there is no contention in this case that either a chemist or an oncologist would understand the actual claim language (particularly "method for administering") differently from the other. Both would equally understand the obvious point that a "method for administering" a drug differs from a "method for treating" a disease, and that the '209 patent's claims concern the former. Indeed, Lilly specifically cancelled or forwent claims to the goals of inhibiting

tumor growth or reducing toxicity, and chose instead to claim only "method[s] for administering."

Under *Warner-Jenkinson*, *Festo*, and this Court's precedent, Lilly's choice to claim "method[s] for administering" cannot be brushed aside and equivalence analyzed as if the claim language were something different or as if the specific words did not matter.

Once the focus is properly on the claimed "method for administering," then differences in solubility, stability, pH, and buffering capacity cannot be dismissed out of hand as "irrelevant." Appx18. As a factual matter, the differences themselves are undisputed. Appx11 ("The parties disagree on the *relevance* of any chemical differences …. nevertheless both Lilly's and Dr. Reddy's experts … *agreed on what the differences were*."); Appx18 (similar). Giving those differences their legally required due in light of the actual claim language requires reversal of the infringement judgment. *Warner-Jenkinson*, 520 U.S. at 39 n.8; *Advanced Steel Recovery*, 808 F.3d at 1319 (quoting *id.*).

CONCLUSION

The district court's infringement judgment should be reversed.

October 9, 2018

Respectfully submitted,

/s/ John C. O'Quinn

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ADDENDUM

Amended Final Judgment Appx1

Entry on Plaintiff's Motion to Amend Final Judgment..... Appx2-6

Final Judgment Appx7-8

Findings of Fact and Conclusions of Law Appx9-22

Summary Judgment Order..... Appx23-44

U.S. Patent No. 7,772,209..... Appx45-54

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,

Plaintiff,

v.

DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.,

Defendants.

No. 1:16-cv-308-TWP-MPB

AMENDED FINAL JUDGMENT

Plaintiff Eli Lilly and Company ("Lilly"), by counsel, having filed its Motion to Amend Final Judgment, and the Court having considered the Motion now finds that it should be granted. Pursuant to the Court's findings of fact and conclusions of law following the bench trial, final judgment is hereby entered as follows:

1. The filing of NDA No. 208297 infringed at least claims 9, 10, 12, 13, 14, 15, 18, 19, 21, and 22 of U.S. Patent No. 7,772,209.

2. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of any product that is the subject of NDA No. 208297 shall be not earlier than the latest date of expiration of U.S. Patent No. 7,772,209, including any period of pediatric exclusivity.

3. JUDGMENT IS ENTERED in favor of Lilly and against Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.

Date: 7/27/2018

Laura A. Briggs, Clerk

BY: _____
Deputy Clerk, U. S. District Court

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

Distribution to all counsel of record via ECF

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 1:16-cv-00308-TWP-MPB
	)	
DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC.,	)	
	)	
Defendants.	)	

ENTRY ON PLAINTIFF'S MOTION TO AMEND FINAL JUDGMENT

This matter is before the Court on Plaintiff Eli Lilly's ("Lilly") Motion to Amend Final Judgment. (Filing No. 244.) Also before the Court is Defendants Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s, (collectively, "Dr. Reddy's") Motion for Leave to File Surreply Brief. (Filing No. 250.) Lilly takes no position on Dr. Reddy's Motion for Leave to File Surreply. (Filing No. 251.) The Court **grants** Dr. Reddy's Motion, and has considered its Surreply.[1] For the reasons stated below, the Court determines that Lilly's Motion to Amend Final Judgment is **granted**.

I. BACKGROUND

On February 5, 2016, Lilly filed a Hatch-Waxman patent infringement action against Dr. Reddy's following Dr. Reddy's submission of a New Drug Application ("NDA") seeking approval to market a pemetrexed ditromethamine product. (Filing No. 1.) Lilly alleged that Dr. Reddy's product infringed upon its U.S. Patent No. 7,772,209 ("209 Patent") on its ALTIMA® cancer

[1] The Court agrees with Dr. Reddy's that new arguments were made in Lilly's Reply Brief, and therefore has considered Dr. Reddy's surreply to address these arguments. A party may seek leave from the court to file a surreply to address new matters argued in the reply brief. *Heckler & Koch, Inc. v. German Sport Guns GmbH*, No. 1:11-CV-1108-SEB-TAB, 2013 WL 2406262, at *3 (S.D. Ind. May 31, 2013).

chemotherapy product, which uses pemetrexed disodium. A bench trial was held beginning on February 1, 2018 and concluding on February 2, 2018.

On June 22, 2018, the Court entered a Final Judgment in favor of Lilly. (Filing No. 242.) The Court found that Dr. Reddy's product infringed Lilly's product under the doctrine of equivalents. The Final Judgment stated that, "Judgment is entered in favor of Plaintiff Eli Lilly & Co. and against Defendant Dr. Reddy's Inc. and this action is TERMINATED." *Id*. On June 27, 2018, Lilly filed the pending Motion to Amend Final Judgment (Filing No. 244) requesting an amendment which would provide particular relief as follows:

> 1. The filing of NDA No. 208297 infringed at least claims 9, 10, 12, 13, 14, 15, 18, 19, 21, and 22 of U.S. Patent No. 7,772,209.
>
> 2. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of any product that is the subject of NDA No. 208297 shall be not earlier than the latest date of expiration of U.S. Patent No. 7,772,209, including any period of pediatric exclusivity.
>
> 3. JUDGMENT IS ENTERED in favor of Lilly and against Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.

Filing No. 244-1. Dr. Reddy's objects to the Motion.

II. DISCUSSION

Dr. Reddy's asserts three bases for denying Lilly's Motion to Amend Final Judgment: 1) the amendment is unnecessary and would give Lilly an unjustified windfall; 2) the Court is not required to grant the relief sought by Lilly; 3) Lilly's enumeration of the asserted claims is inaccurate and overbroad. In turn, Lilly responds that the Hatch-Waxman Act requires this Court to amend the Final Judgment in accordance with Lilly's proposal. Lilly seeks to amend the Final Judgment to order resetting the effective date of approval of Dr. Reddy's product to a date not earlier than the date of the expiration of the patent which has been infringed (including pediatric exclusivity). (Filing No. 248 at 1.)

The relevant statute reads:

> (4) For an act of infringement described in paragraph (2)—
>
> > (A) the court *shall* order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
> >
> > (B) injunctive relief *may* be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product,
> > ….

35 U.S.C. § 271(e)(4) (emphasis added). Relying on *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011 (N.D. Ill. 2003), Dr. Reddy's contends that 35 U.S.C. § 271(e)(4) "*permits* the Court to order delay of approval sought by Lilly but does not *require* the Court to do so." (Filing No. 247 at 2) (emphasis in original). Moreover, Dr. Reddy's asserts that because it has already agreed not to launch its product commercially until the expiration of the '209 Patent or a successful appeal, the Court need not grant Lilly any further relief. Lilly responds that the statutory language including the word "shall" requires that the Court reset the effective date of any approval, which is sufficient to resolve this case. The Court agrees. Although by the terms of the statute, injunctive relief is a discretionary remedy, resetting the effective date of approval is mandatory. The Federal Circuit has addressed this issue. "Accordingly, upon a finding of patent infringement under § 271(e)(2), the district court must order remedies in accordance with § 271(e)(4)." *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1138 (Fed. Cir. 2018). Lilly notes that the policy justification for this procedure is due to the fact that the Food and Drug Administration (the "FDA") is not a party to Hatch-Waxman patent litigation. Congress vested district courts with the role of ordering the FDA, as a non-party, to take action in compliance with the order when a proposed product is found to infringe. (Filing No. 248 at 6.) Because resetting

the effective date for approval is not a discretionary decision, the Court need not address Dr. Reddy's argument that the amendment is unnecessary and gives Lilly a windfall based on bureaucratic delay at the FDA.

Next, Dr. Reddy's argues that Lilly's enumeration of the asserted claims is inaccurate and overbroad because it includes additional claims that were not asserted against Dr. Reddy's by reciting the words "at least" before the enumerated claims. (Filing No. 247 at 3.) Lilly does not object to striking the words "at least" before the enumerated claims, but notes that dependent claims necessarily would also be found to have been infringed based on the interconnected relationships of the claims, regardless if the claims were not asserted at trial. The Court declines to strike the words "at least" from the amendment in an effort for consistency to parallel other judgments this Court has entered. Case No. 1:12-cv-00086-TWP-MPB, ECF 87 (Accord), ECF 98 (Apotex); Case No. 1:16-cv-00469-TWP-MPB, ECF 28 (Biocon); Case No. 1:14-cv-00104-TWP-MPB, ECF 45 (Glenmark); Case No. 1:16-cv-03460-TWP-MPB, ECF 94 (Hospira); Case No. 1:13-cv-01469-TWP-DKL, ECF 57 (Sun).

III. CONCLUSION

For the reasons stated above, the Court **GRANTS** Lilly's Motion to Amend Final Judgment (Filing No. 244) and **accepts** Lilly's proposed order (Filing No. 244-1). An amended entry of final judgment will follow in a separate order. The Court **grants** Dr. Reddy's Motion (Filing No. 250), and has considered its Surreply.

SO ORDERED.

Date: 7/27/2018

Tanya Walton Pratt

TANYA WALTON PRATT, JUDGE
United States District Court
Southern District of Indiana

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
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ELI LILLY AND COMPANY,	)	
	)	
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v.	)	Case No. 1:16-cv-00308-TWP-MPB
	)	
DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC.,	)	
	)	
Defendants.	)	

FINAL JUDGMENT PURSUANT TO FED. R. CIV. PRO. 58

The Court having this day made its Entry directing the entry of final judgment, the Court now enters **FINAL JUDGMENT**.

Judgment is entered in favor of Plaintiff Eli Lilly & Co. and against Defendant Dr. Reddy's Inc. and this action is **TERMINATED**.

IT IS SO ORDERED.

Date: 6/22/2018

TANYA WALTON PRATT, JUDGE
United States District Court
Southern District of Indiana

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v.	)	Case No. 1:16-cv-00308-TWP-MPB
	)	
DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC.,	)	
	)	
Defendants.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW FOLLOWING FEBRUARY 1, 2018 BENCH TRIAL

This matter was before the Court for a bench trial beginning on February 1, 2018 and concluding on February 2, 2018, on the issue of infringement of U.S. Patent No. 7,772,209 (the "'209 Patent"). This is a Hatch-Waxman patent infringement action brought by Eli Lilly and Company ("Lilly"), the owner of the '209 Patent, against Defendants Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "Dr. Reddy's") arising out of Dr. Reddy's filing of New Drug Application No. 208297 (the "NDA") with the Food and Drug Administration ("FDA") seeking approval to market the product described therein. The '209 Patent describes a method of administering a chemotherapy drug, pemetrexed disodium ("pemetrexed"), with vitamins, which is marketed by Lilly under the trade name ALITMA®. Lilly is asserting that Dr. Reddy's drug product, which uses pemetrexed ditromethamine, infringes the '209 Patent. Dr. Reddy's contends that its product is not a generic drug, rather, its product uses a different chemical. Particularly at issue is claim 12. The Court previously constructed claim 12 to refer to a liquid administration of pemetrexed disodium. (Filing No. 199 at 9.) Having heard testimony and

considered the exhibits and arguments of the parties, the Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. FINDINGS OF FACT

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 sells pemetrexed in the United States under the trademark ALIMTA® for treatment of patients with malignant pleural mesothelioma, or for the initial treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer, and other forms of lung cancer. 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.

Dr. Reddy's Ltd. is a drug manufacturer with a principal executive office at Hyderabad, Telangana 500 034, India, and Dr. Reddy's Inc. is a corporation organized and existing under the laws of the State of New Jersey. Dr. Reddy's is in the business of manufacturing, marketing, and selling both generic and non-generic drug products. In December 2015, Dr. Reddy's notified Lilly that it had submitted to the FDA New Drug Application No. 208297, a product that will be marketed as competing products to ALIMTA®

Dr. Clet Niyikiza ("Dr. Niyikiza"), the inventor of the '209 Patent, 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. The problem the invention solves is toxicity in patients receiving chemotherapeutic treatment with pemetrexed. In particular, the '209 Patent provides for a method that mitigates the

toxicity associated with pemetrexed treatment, using the vitamin pretreatment regimen of vitamin B_{12} and folic acid. (Filing No. 231 at 35.)

The primary focus of this infringement trial is on whether Dr. Reddy's label, specifically the use of pemetrexed ditromethamine product described therein, infringes the '209 Patent, which uses pemetrexed disodium, under the doctrine of equivalents. 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®. Claim 12 of the '209 Patent describes an improved method for administering pemetrexed disodium, comprising "a) administration of between 3500 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium; b) administration of about 500 µg to about 1500 µg of vitamin B_{12}, prior to the first administration of pemetrexed disodium; and c) administration of pemetrexed disodium." (Filing No. 1-1 at 9).

The parties disagree on the relevance of any chemical differences between pemetrexed disodium and pemetrexed ditromethamine, nevertheless both Lilly's and Dr. Reddy's experts, Dr. Bruce A. Chabner, M.D., ("Dr. Chabner"), Rodolfo Pinal ("Dr. Pinal"), and George Gokel ("Dr. Gokel"), agreed on what the differences were between the two chemical compounds. Sodium is an inorganic metallic salt, and tromethamine is an organic, nonmetallic salt. (Filing No. 231 at 181.) Tromethamine weighs more than sodium. *Id.* Because tromethamine can raise pH, it can be used as buffer; however, sodium may not be used as a buffer because it cannot be used as a pH adjuster. *Id.* at 158. Additionally, it is undisputed that pemetrexed disodium is more hygroscopic and absorbs more than twice the amount of water than pemetrexed ditromethamine. *Id.* at 173. As noted in the Court's claim construction finding, regardless if pemetrexed disodium or pemetrexed ditromethamine is administered to the patient, the patient receives an intravenous

solution of pemetrexed in treating the patient's cancer. The evidence presented at trial demonstrates that the person who solves the problems to which the claims are addressed requires a medical oncologist.

II. CONCLUSIONS OF LAW

A. Prosecution History Estoppel

In the Court's amended Final Pretrial Entry, the Court permitted the parties, at trial, to supplement the summary judgment record on the issue of prosecution history estoppel. (Filing No. 216 at 4.) In its Entry on Motion for Summary Judgment of Noninfringement, the Court found Lilly was not barred, as a matter of law under prosecution history estoppel, from asserting the doctrine of equivalents. (Filing No. 199 at 15.) ("Lilly has met its burden of showing that it did not surrender the equivalent in question because the choice of pemetrexed salt is tangential to the reasons for the amendment and summary judgment is precluded on this issue.")

As in the summary judgment briefing, Dr. Reddy's continues to collapse the foreseeability exception with the tangential exception, on which the Court relied in holding in Lilly's favor. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002). Dr. Reddy's focuses on the unexplained reason that Lilly limited the '209 Patent to pemetrexed disodium, in essentially arguing that Lilly could have drafted a better claim. ("[A]" patentee cannot argue in litigation that a narrowing amendment in prosecution was excessive, and that the patentee could have avoided the prior art (and gained allowance) with a less severe amendment that would have literally embraced the accused equivalent." (Filing No. 234 at 6).) In any event, Lilly has explained the reason for the narrowing amendment: it was narrowed to overcome a rejection in view of Arsenyan, a prior art article about a different antifolate, methotrexate. (Filing No. 235 at 35.) The Court agrees with Lilly that at trial Dr. Reddy's expert, Dr. Gokel, did nothing to dispute or add to

the summary judgment record as to the prosecution history evidence from which tangentiality is analyzed. (Filing No. 232 at 42.) Accordingly, the Court again concludes that Lilly's rationale for limiting its claim to pemetrexed disodium (to avoid a rejection based on the prior art Arsenyan) is tangential to the accused equivalent—pemetrexed ditromethamine. The Court directs the parties to Filing No. 199 for a more detailed analysis regarding the Court's holding that Lilly has rebutted the presumption that prosecution history estoppel applies.

B. Disclosure-Dedication Rule

Another issue, extensively briefed by the parties on summary judgment, was the disclosure-dedication doctrine. Again, the trial record and the summary judgment record contain significant overlap as to this issue. Because Lilly did not move for summary judgment on this issue, it was not decided on summary judgment, rather it was fleshed out by expert testimony at the trial. The disclosure-dedication rule bars a doctrine of equivalents claim when a patentee discloses but does not claim subject matter. *Johnson & Johnston Associates, Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

As noted in the Court's Entry on Motion for Summary Judgment of Noninfringement, it is undisputed that the '209 Patent's specification did not expressly disclose pemetrexed ditromethamine. Rather, Dr. Reddy's bases its disclosure-dedication argument on the fact that the '209 Patent referenced U.S. Patent No. 4,997,838 to Akimoto and that from Akimoto the hypothetical person of skill in the art ("POSA") could find pemetrexed ditromethamine disclosed among the alternatives disclosed in Akimoto. (Filing No. 234 at 25-26.) Generic references in a written specification do not necessarily dedicate all members of a particular genus to the public. *SanDisk Corp. v. Kingston Technology Co., Inc.*, 695 F.3d 1348, 1363 (Fed. Cir. 2012).

> Rather, the 'disclosure must be of such specificity that one of ordinary skill in the art could identify the subject matter that had been disclosed and not claimed.'

> Additionally, in *Pfizer Inc. v. Teva Pharmaceuticals, USA, Inc.*, 429 F.3d 1364 (Fed. Cir. 2005), this court further clarified that 'before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation.'

Id. (citations omitted). Although the '209 Patent did not expressly incorporate Akimoto by reference, it cited that preferred examples of antifolates can be found in the derivatives described by Akimoto. (Filing No. 1-1 at 5.) Because this issue hinged on what a POSA would recognize as unclaimed subject matter disclosed in the '209 Patent specification and if Akimoto's disclosures in combination would disclose pemetrexed ditromethamine, it left a factual dispute for trial.

At trial, Dr. Pinal testified that Akimoto included pemetrexed and any "pharmaceutically acceptable salt thereof." (Filing No. 231 at 249.) From this concession, Dr. Reddy's argues that pharmaceutically accepted salts would include substituted ammonium salts of which tromethamine is one of a few FDA-approved substituted ammonium salts. (Filing No. 234 at 24.) Thus, Dr. Reddy's contends that a POSA would have recognized pemetrexed in combination with tromethamine as an alternative to pemetrexed disodium. (Filing No. 234 at 26-27.) Lilly responds that while Dr. Pinal testified that pemetrexed is within the genus covered by Akimoto, Dr. Pinal also testified that Akimoto disclosed a genus of thousands of antifolates. (Filing No. 231 at 227.) Further, tromethamine is not specifically disclosed in any referenced patent nor is the compound pemetrexed ditromethamine. (Filing No. 238 at 16-17.) Because Akimoto was not expressly incorporated, as required, in the '209 Patent, and in any event Akimoto does not specifically disclose pemetrexed ditromethamine as an alternative to pemetrexed disodium, the disclosure-dedication rule does not bar Lilly's doctrine of equivalents claim. At most, the reference to Akimoto and what was contained therein amounts to a generic reference which does not dedicate all members of a particular genus to the public.

C. Doctrine of Equivalents

Lilly asserts, and the Court agrees, that healthcare providers using the proposed Dr. Reddy's product will directly infringe under the doctrine of equivalents, and that Dr. Reddy's is liable as an indirect infringer under 35 U.S.C. §§ 271(b) and (c).

As an initial matter, the relevant POSA must be defined for a doctrine of equivalents analysis. "What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24 (1997) (citation omitted). Thus, a POSA becomes an important factor as to "whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." *Id.* Dr. Reddy's contends that the POSA should be the type of person who solves the problems to which the claims are addressed such as Dr. Niyikiza, the inventor of the patent.[1] (Filing No. 234 at 28, 30.) ("The POSA could be trained as a chemist, biochemist, pharmaceutical scientist, physician, or molecular biologist. The POSA, even if he is a physician, should have a strong background in chemistry and biochemistry, understand the folate pathways and metabolism, and have a solid grasp of acid-base.") Dr. Reddy's proposed POSA would examine the doctrine of equivalents from the perspective of the chemical and biochemical properties between pemetrexed disodium and pemetrexed ditromethamine. (Filing No. 234 at 30.) Lilly responds that the '209 Patent makes clear, from the plain language of the claims and testimony from the inventor, Dr. Niyikiza, that the POSA is directed to a medical oncologist. (Filing No. 235 at 13.) Lilly's proposed POSA would perform a doctrine of equivalents analysis focusing on the medical treatment aspects of the claims. (Filing No. 238 at 19.) This Court has "previously defined the POSA as 'a medical doctor who specializes in

[1] Dr. Niyikiza is a statistician, with a Ph.D. in mathematics and statistics, not a chemist, biochemist, pharmaceutical scientist, physician, or molecular biologist. (Filing No. 238 at 21.)

oncology or a medical doctor with extensive experience in the areas of nutritional sciences involving vitamin deficiencies [,who] collaborated with medical oncologists who have knowledge and experience in the treatment of cancer through the use of antifolates.'" *Eli Lilly and Company v. Teva Parenteral Meds., Inc.*, 1:10-cv-1376-TWP-MPB, 2012 WL 2358102, at *4 (S.D. Ind. June 20, 2012), ECF 115 at 8. Essentially, the point of contention between the proposed POSAs advanced by the parties is whether the POSA is a chemist or an oncologist.

Dr. Reddy's POSA definition is defeated by the plain language of the '209 Patent as the invention explicitly identifies it as "a method of reducing the toxicity associated with the administration of an antifolate to a mammal. . ." (Filing No. 1-1 at 5). Lilly is correct that the relevant POSA who works to mitigate the toxicities of chemotherapy would be an oncologist, particularly an oncologist with extensive experience in the areas of nutritional sciences involving vitamin deficiencies as confirmed by Dr. Chabner. Thus, equivalency is examined from an oncologist POSA. The relevant POSA is critical (and dispositive) to resolving the doctrine of equivalents analysis in the context of the claims as to whether the POSA would focus on the different salt forms of pemetrexed disodium and pemetrexed ditromethamine as being substantial differences, or instead would focus on the pemetrexed treatment that the patient receives.

The United States Supreme Court has set out two frameworks for evaluating equivalence—the function, way, result test (whether the accused product performs 'substantially the same function in substantially the same way to obtain the same result'), and the insubstantial differences test (whether the accused product or process is substantially different from what is patented). *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866–67 (Fed. Cir. 2017) ("Thus, the Court seemingly blessed two equivalents tests, leaving to the lower courts in future cases the choice of which to apply.") (quoting *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S.

605, 608 (1950). Additionally, the Federal Circuit, relying on *Graver*, noted that the insubstantial differences test may be more appropriate in chemical arts cases. *Id.* ("The Supreme Court was surely correct in stating that non-mechanical cases may not be well-suited to consideration under the FWR test.") Because equivalence in this case is based on chemical properties, the Court determines that the insubstantial differences test is the more appropriate framework for evaluating equivalence.

"Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003). "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002). As noted previously, the relevant POSA, in this case, is a medical oncologist. Dr. Chabner testified that the invention claimed in the '209 Patent relates to "using pretreatment B_{12} and folic acid to mitigate the toxicity of pemetrexed when it's given to a patient with cancer." (Filing No. 231 at 70.) Additionally, Dr. Chabner testified that the pemetrexed disodium could not exert an anti-cancer effect in solid form, thus the POSA would understand that pemetrexed disodium is administered by first putting it into solution and then intravenously administering the solution to the patient for an anti-cancer effect. *Id.* at 72.

Under the relevant context that the claim relates to medical treatment, pemetrexed ditromethamine treats the patient's cancer in exactly the same way as pemetrexed disodium. It is undisputed that when both pemetrexed disodium and pemetrexed ditromethamine are placed in solution, that both compounds dissociate completely in solution resulting in free pemetrexed and

therapeutically irrelevant counterions. *Id.* at 208-09. In fact, in aqueous solution, the two products will be identical. (Filing No. 231 at 212.) Recognizing these similarities, Dr. Reddy's relied on Lilly's clinical trials of pemetrexed disodium, in demonstrating the safety and efficacy of its product, when it told the FDA that the salt form does not matter when it comes to treating the patient to support approval of its NDA product. (Filing No. 231 at 80-81.) It is undisputed that the products are bioequivalent; however, the parties disagree on whether there is patent equivalence in the context of the claimed method. (Filing No. 234 at 42-43; Filing No. 238 at 24.) "[W]hen a commercial product meets all of the claim limitations, then a comparison to that product may support a finding of infringement." *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1289 (Fed. Cir. 2010).

The differences in the chemical properties between pemetrexed disodium and pemetrexed ditromethamine with regards to solubility, stability, pH, and buffering capacity are irrelevant in the context of the claimed method including this Court's claim construction. (Filing No. 234 at 42.) Additionally, the theoretical phenomenon of the difference of salting out between the two products is irrelevant, as ALIMTA®'s label "requires the solution to be clear prior to administration and specifically instructs physicians not to administer it if any particulate matter is observed." (Filing No. 235 at 22-23.) To be sure, the evidence shows that tromethamine differs from sodium with regards to the chemical properties as alleged by Dr. Reddy's. Lilly does not dispute that there are differences when the products are in solid form, instead Lilly argues that the differences are insubstantial. (Filing No. 231 at 80.) The Court agrees. The differences are irrelevant in the context of the claimed method which is a liquid administration of pemetrexed sodium. What is in fact ultimately administered to the patient is injectable pemetrexed ions that enter the patient's cells. (Filing No. 231 at 79-80.) The products are identical in liquid form as

pemetrexed is the active moiety in both Dr. Reddy's and Lilly's products dissolved in solution. (*See* Filing No. 232 at 124-25; Filing No. 235 at 18.) Furthermore, Dr. Reddy's incorrectly relies on a chemist POSA in posing nonequivalence, who would not administer the drugs to a patient as the '209 Patent is a claimed method of treatment. Accordingly, Lilly has shown by a preponderance of the evidence that Dr. Reddy's product is equivalent to Lilly's product.

D. Inducement and Contribution to Infringement of '209 Patent

A party can be held liable for indirect infringement by actively inducing or contributing to direct infringement by others. 35 U.S.C. § 271(b), (c). Direct infringement occurs when one party makes, uses, offers to sell, sells, or imports each element of a patented invention. 35 U.S.C. § 271(a). Because Dr. Reddy's does not provide care to patients, the direct infringement is attributed to the healthcare providers.

"Inducement requires that the alleged infringer knowingly induced infringement and possessed a specific intent to encourage another's infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). Courts have inferred intent to induce infringement based on the contents of labels. *Id.* (holding circumstantial evidence may suffice to prove specific intent to induce infringement). Similarly, labels may also form the basis to infer intent under contributory infringement when they instruct users to perform a patented method. *See Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011).

Relying on *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1928 (2015), Dr. Reddy's contends that Lilly cannot prove Dr. Reddy's specifically intended to infringe because specific intent requires proof that Dr. Reddy's knew the acts were infringing. (Filing No. 234 at 44.) As evidence that Dr. Reddy's did not know its product would infringe the '209 Patent, Dr. Reddy's offers that it selected tromethamine, in good-faith belief, to avoid infringing the '209

Patent. *Id.* at 45. As Lilly correctly points out, Dr. Reddy's ignores how specific intent can be shown in the Hatch-Waxman context, particularly how specific intent can be inferred from an accused product's labeling. *AstraZeneca LP v. Apotex, Inc.* considered similar facts where Apotex's product development team testified that it "never intended to instruct or encourage either physicians or patients to use its generic drug once-daily." *Id*. However, AstraZeneca held "[t]he pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of Apotex's affirmative intent to induce infringement." *Id.* at 1060. Specific intent and liability for inducement are established if "the product labeling that Defendants seek would inevitably lead some physicians to infringe." *Eli Lilly and Company v. Teva Parenteral Meds., Inc.,* 845 F.3d 1357, 1368-69 (Fed. Cir. 2017); *Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp., 758 F.3d 625, 631 (Fed. Cir. 2015)*. Dr. Reddy's has provided no defense to the infringing pretreatment regimen portion of its label that this Court has already found induced infringement in another case with label instructions substantively identical to those in Dr. Reddy's Label. *Eli Lilly and Company v. Teva Parenteral Meds., Inc.,* No.1:10-cv-1376-TWP-MPB, 126 F.Supp.3d 1037 (S.D. Ind. Aug. 25, 2015).

As noted previously, administration of pemetrexed ditromethamine according to Dr. Reddy's label infringes Lilly's product under the doctrine of equivalents. In a Hatch-Waxman case such as this, infringement "is focused on the product that is likely to be sold following FDA approval," including the relevant knowledge of the parties at the time the product is sold. *See Abbott Laboratories v. TorPharm, Inc.,* 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("This determination is based on consideration of all the relevant evidence, including the ANDA filing, other materials submitted by the accused infringer to the FDA, and other evidence provided by the parties."). "We have long held that the sale of a product specifically labeled for use in a patented method

constitutes inducement to infringe that patent, and usually is also contributory infringement." *Eli Lilly & Co. v. Actavis Elizabeth LLC,* 435 F. App'x 917, 926 (Fed. Cir. 2011) (citing *AstraZeneca LP v. Apotex, Inc.,* 633 F.3d 1042, 1060 (Fed.Cir.2010)).

This Court has determined that Dr. Reddy's product infringes the '209 Patent under the doctrine of equivalents. Accordingly, it cannot avoid intent or infringement on the bases that it possessed a "good faith belief that its proposed product[s] would not infringe." Moreover, the Court finds, based on a preponderance of the evidence, Dr. Reddy's label instructs users to perform the patented method by both inducing and contributing to infringement and that Dr. Reddy's had the requisite specific intent and knowledge that its label would cause such infringement. Dr. Reddy's product does not have a substantial noninfringing use to avoid contributory infringement. A physician administering Dr. Reddy's product would constitute direct infringement under § 271(a); thus, the use the Dr. Reddy's NDA products would constitute inducement and contributory infringement of the '209 Patent by Dr. Reddy's under 35 U.S.C. § 271(b), (c).

III. CONCLUSION

Based upon the foregoing findings of fact and conclusions of law, the Court concludes that Lilly has shown by a preponderance of the evidence that the asserted claims of the '209 Patent would be infringed by Dr. Reddy's product under the doctrine of equivalents based upon inducement and contributory infringement. The Court finds that Dr. Reddy's product indirectly infringes the asserted claims of the '209 Patent, and finds in favor of Eli Lilly And Company and against Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.. Final judgment shall issue separate from this Entry.

SO ORDERED.

Date: 6/22/2018



TANYA WALTON PRATT, JUDGE
United States District Court
Southern District of Indiana

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 1:16-cv-00308-TWP-MPB
	)	
DR. REDDY'S LABORATORIES, LTD., and DR. REDDY'S LABORATORIES, INC.,	)	
	)	
Defendants.	)	

ENTRY ON MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

This matter is before the Court on Defendants Dr. Reddy's Laboratories, LTD.'s and Dr. Reddy's Laboratories, Inc.'s (collectively, "Dr. Reddy's") Motion for Summary Judgment of Noninfringement of the U.S. Patent 7,772,209 (the "'209 Patent") (Filing No. 132). Plaintiff Eli Lilly and Company ("Lilly") initiated this Hatch-Waxman litigation alleging that Dr. Reddy's New Drug Application No. 208297 and the use of the product described therein, infringe Lilly's '209 Patent. On November 9, 2017, oral argument was held on the Motion at which the parties made helpful presentations. For the reasons stated below, the Court determines that summary judgment is not appropriate and Dr. Reddy's Motion is **denied**.

I. BACKGROUND

The '209 Patent describes a method of administering a chemotherapy drug, pemetrexed disodium, with a pretreatment regimen of vitamin B_{12} and folic acid ("pretreatment regimen"), which is marketed by Lilly under the trade name ALIMTA®. The '209 Patent has been the subject of two previous trials before this Court. *See Eli Lilly and Co. v. Teva Parenteral Medicines, Inc.*, 126 F. Supp.3d 1037, 1038 (S.D. Ind. 2015)[1]. Those cases specifically concerned generic drug

[1] The '209 Patent is also the subject of other pending infringement suits pending before this Court.

manufacturers that sought to market a generic version of ALIMTA® including labeling that induced physicians to direct patients to take folic acid and vitamin B_{12} in accordance with the pretreatment claims in the '209 Patent. Specifically, in the *Teva* case, the pretreatment regimen and whether the steps of the claimed method could be attributed to a single actor was at issue. *Id.*

During prosecution of its patent application for ALIMTA®, the U.S. Patent and Trademark Office originally rejected claim 2 of the '209 Patent as being anticipated by a prior art article, Arsenyan et.al. ("Arsenyan"). Arsenyan concerned the administration of the compound methotrexate.[2] To avoid rejection of its patent in view of Arsenyan, Lilly narrowed the scope of its claims from a broad category of antifolates to specifically pemetrexed disodium. (Filing No. 133-1 at 124; Filing No. 146 at 30.)

Dr. Reddy's is a drug manufacturer and does not treat patients, therefore any infringement would be based on indirect infringement. Dr. Reddy's set out to avoid infringing the '209 Patent by designing a different product. It ran experiments to investigate different salts, and chose tromethamine. Unlike the generic drug manufacturers that used pemetrexed disodium in the proposed generic drugs in previous trials, Dr. Reddy's seeks to market a new product that uses pemetrexed ditromethamine, rather than pemetrexed disodium.

A point of contention between the parties is whether pemetrexed ditromethamine was excluded (thus designated public use) from the claims during patent prosecution by Lilly's specification and narrowing amendment from the term "antifolates" to "pemetrexed disodium." Tromethamine is an inorganic, metallic salt, whereas sodium is an organic, nonmetallic salt.

[2] Both methotrexate and pemetrexed fall within the broader antifolate group, but they target different enzymes. (Filing No. 146 at 44.)

(Filing No. 135 at 8.) The liquid solution of both chemical compounds results in pemetrexed treatment, but the powdered solid form of the two products differ as a result of the different salt compounds used. The patient receives the liquid solution intravenously. The products are sold in solid form. At issue is claim 12 of the '209 Patent. Claim 12 reads as follows:

> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
>
> a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium
>
> b) administration of about 500 µg to about 1500 µg of vitamin B_{12}, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

(Filing No. 1-1 at 9).

As previously noted, Dr. Reddy's product uses a different pemetrexed compound: pemetrexed ditromethamine. In addition, Dr. Reddy's label on the administration of the pemetrexed ditromethamine differs from Lilly's in that Dr. Reddy's label instructs that pemetrexed ditromethamine should be reconstituted and diluted with 5% dextrose in water ("dextrose"), whereas Lilly's label instructs that the pemetrexed disodium should be reconstituted and diluted in saline solution. (Filing No. 92-3; Filing No. 179-1.) Dr. Reddy's label states "[c]oadminstration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended." (Filing No. 92-3 at 9.) Dr. Reddy's label also instructs that the pretreatment regimen be followed and mitigates the severe toxicities that pemetrexed can otherwise cause. *Id.* at 42.

Both Dr. Reddy's and Lilly's labels indicate that its products are to be administered along with cisplatin for some patients. *Id.* at 11. Before cisplatin can be administered to a patient it requires and is standard practice to prehydrate it with saline to prevent serious kidney toxicity. (Filing No. 146 at 13-14.) Dr. Reddy's label instructs that the cisplatin be administered intravenously approximately thirty minutes after the end of administration of pemetrexed treatment. (Filing No. 92-3 at 37.) Saline is commonly used in intravenous administration for many different drugs.

II. LEGAL STANDARD

The purpose of summary judgment is to "pierce the pleadings and to assess the proof in order to see whether there is a genuine need for trial." *Matsushita Electric Industrial Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986). Federal Rule of Civil Procedure 56 provides that summary judgment is appropriate if "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." *Hemsworth v. Quotesmith.Com, Inc.*, 476 F.3d 487, 489-90 (7th Cir. 2007). In ruling on a motion for summary judgment, the court reviews "the record in the light most favorable to the nonmoving party and draw[s] all reasonable inferences in that party's favor." *Zerante v. DeLuca*, 555 F.3d 582, 584 (7th Cir. 2009) (citation omitted). However, "[a] party who bears the burden of proof on a particular issue may not rest on its pleadings, but must affirmatively demonstrate, by specific factual allegations, that there is a genuine issue of material fact that requires trial." *Hemsworth*, 476 F.3d at 490 (citation omitted). "In much the same way that a court is not required to scour the record in search of evidence to defeat a motion for summary judgment, nor is it permitted to

conduct a paper trial on the merits of a claim." *Ritchie v. Glidden Co.*, 242 F.3d 713, 723 (7th Cir. 2001) (citation and internal quotations omitted). Finally, "neither the mere existence of some alleged factual dispute between the parties nor the existence of some metaphysical doubt as to the material facts is sufficient to defeat a motion for summary judgment." *Chiaramonte v. Fashion Bed Grp., Inc.*, 129 F.3d 391, 395 (7th Cir. 1997) (citations and internal quotations omitted).

III. DISCUSSION

As an initial matter, the Court notes that Lilly recently changed its ALIMTA® label in response to the Food and Drug Administration's ("FDA") instructions to change various aspects of the label. Nevertheless, both parties agree that the new label does not change the substance or legal theories of any of the briefings previously submitted to the Court and that the parties are prepared to go forward with the proceedings as they currently stand. (Filing No. 182 at 7-10.)

Lilly argues that Dr. Reddy's product infringes under two theories: literal infringement and the doctrine of equivalents. (Filing No. 146 at 19.) The Court will first address the embedded claim construction issue and then address each infringement theory.

A. Claim Construction

The claims define the scope of patent protection. *Johnson & Johnston Associates, Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002). The words of a claim are generally given their ordinary and customary meaning, as understood by a person of skill in the art ("POSA") when the patent was filed. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc)*. When the ordinary meaning of a claim is disputed, the Federal Circuit has directed courts to look to the patent specification, which is the single best guide to the meaning of a disputed term. *Id.* at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

"The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1316. Courts may also consider extrinsic evidence, such as expert testimony or dictionaries, but such evidence is "less significant" than the patent specification and prosecution history (*i.e.*, the written history of patentee's prior dealings with the patent office). *Id.* at 1317. "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* "[I]t is necessary to consider the specification as a whole, and to read all portions of the written description, if possible, in a manner that renders the patent internally consistent." *Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369, 1379-80 (Fed. Cir. 2001). "A claim construction that excludes a preferred embodiment. . .is rarely, if ever correct." *SanDisk Corp. v. Memorex Products, Inc.*, 415 F. 3d 1278, 1285 (Fed. Cir. 2005) (citation and internal quotation omitted).

At the hearing, the parties set forth different constructions of claim 12's meaning. (*See* Filing No. 182 at 23, 30.) It is undisputed that claim 12 is a method claim, but the parties essentially dispute the meaning of "administration of pemetrexed disodium." Lilly argues that "administration of pemetrexed disodium" refers to the act of giving the patient the liquid solution of pemetrexed disodium after it has been diluted and reconstituted because no salt form is given to patients. (Filing No. 182 at 30.) Lilly explains that its experts have opined that a POSA would understand claim 12 to embrace the meaning of a solution with pemetrexed ions and two sodium ions that is given to patients intravenously. *Id.* Dr. Reddy's argues that this construction would

improperly require "changing each instance of 'pemetrexed disodium' in the claims to a 'solution comprising pemetrexed ions and sodium ions.'" (Filing No. 167 at 3.)

"Claim construction begins with the language of the asserted claims." *SanDisk,* 415 F.3d at 1284 (citation omitted). As stated previously the relevant asserted claim at issue is "administration of pemetrexed disodium". The dispute between the parties' different claim construction arguments turns on the word "administration". This is primarily due to the fact that the patient receives the product through a liquid solution, but ALIMTA® is sold in solid or salt form.[3]

The Federal Circuit prefers intrinsic evidence over extrinsic evidence in construing claims. *See Phillips*, 415 F.3d at 1317 ("However, while extrinsic evidence 'can shed useful light on the relevant art,' we have explained that it is 'less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'"") (citations omitted). Turning to the intrinsic evidence first, the Court begins with the specification. The specification must conclude with the claims "particularly pointing out and distinctly claiming the subject matter" which the applicant regards as his invention. *See* 35 U.S.C. §112. This apprises the public of the metes and bounds of the subject matter for which the inventor seeks patent protection.

The '209 Patent's specification distinctly claims pemetrexed disodium. The prosecution history is consistent with this result. "The court must always consult the prosecution history, when offered in evidence, to determine if the inventor surrendered disputed claim coverage." *SanDisk,* 415 F.3d at 1286. Here, the prosecution history reveals that the amendments to the detailed

[3] Although Dr. Reddy's product is not on the market yet, it is also being proposed to sell in a solid form.

description section of the specification as well as the claims were made in response to the U.S. Patent and Trademark Office's ("Patent Office") rejections. (Filing No. 133-1 at 147-48.) Lilly limited the chemical compound used in claim 12 to pemetrexed disodium. "As a basic principle of claim interpretation, prosecution disclaimer promotes the public notice function of the intrinsic evidence and protects the public's reliance on definitive statements made during prosecution. *SanDisk,* 415 F.3d at 1287 (citation omitted).

Unlike pemetrexed disodium, the parties' dispute over the word "administration" is not completely resolved by resorting to intrinsic evidence alone. The specification, claims, nor prosecution history do not resolve this dispute. "There is no 'clear and unmistakable' disclaimer if a prosecution argument is subject to more than one reasonable interpretation, one of which is consistent with a proffered meaning of the disputed term." *Id.* (citation omitted). The '209 Patent does reveal that it is a method invention, but the claims do not address how ALIMTA® *i.e.*, pemetrexed disodium, is actually given to the patient. That requires reading the label's detailed directions. Both products' labels require the powdered form of the drugs to be diluted and reconstituted, using different liquid solvents.[4] The expert reports shed light on what a POSA would understand "administration" to mean. The Court finds it very persuasive that both products are administered in liquid form to be indicative that a POSA would understand the '209 Patent to refer to a method of liquid administration of pemetrexed disodium.

What happens to pemetrexed disodium or pemetrexed ditromethamine after the liquid solution is prepared and administered to the patient is not a question that needs to be resolved in

[4] Lilly's label requires saline, while Dr. Reddy's label requires dextrose.

construing claim 12. In any event, the parties agree on the science of what happens during the administration of the liquid solution the patient. "And Dr. Chabner is saying, well, I think people would understand the claim to mean this. And, basically, what he's saying is, because that makes sense, that's what Lilly should have done, *people know that it's the pemetrexed that matters*." (Filing No. 182 at 51) (emphasis added). The patient receives pemetrexed treatment. "Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, for use in the determination of infringement. It is not an obligatory exercise in redundancy." *U.S. Surgical Corp., v. Ethicon, Inc.,* 103 F.3d 1554, 1568 (Fed. Cir. 1997). Having already determined based on the intrinsic evidence, Lilly claimed "pemetrexed disodium," the Court declines further claim construction based on Lilly's assertion that the term "embraces the administration in liquid form of pemetrexed ions in combination with two sodium ions. (Filing No. 182 at 30.) In sum, the Court construes claim 12's "administration of pemetrexed disodium" language to refer to a liquid administration of pemetrexed disodium. The liquid administration is accomplished by dissolving the solid compound pemetrexed disodium into solution as instructed by the ALIMTA® label. This construction is consistent with the '209 Patent's specification and the plain meaning of claim 12 as well as the prosecution history. It is undisputed that a POSA would understand that the '209 Patent refers to a method of liquid administration because pemetrexed is the active ingredient that treats the cancer and the patient receives the solution intravenously. Further, this construction adheres to the bedrock patent claim construction principle to not exclude a preferred embodiment *i.e.,* pemetrexed disodium, and renders the patent internally consistent.

B. Literal Infringement

"Literal infringement requires a patentee to prove by a preponderance of the evidence that every limitation of the asserted claim is literally met by the allegedly infringing device." *Biovail Corp. Intern. v. Andrx Pharmaceuticals, Inc.*, 239 F. 3d 1297, 1302 (Fed. Cir. 2001). Lilly's theory of literal infringement involves Dr. Reddy's product's use in combination with certain patients that require another chemotherapy drug called cisplatin. In these instances, Dr. Reddy's label instructs that the pemetrexed product is to be infused thirty minutes before cisplatin. Cisplatin requires prehydration with saline solution—sodium chloride. (Filing No. 146 at 2.) Lilly contends that the cisplatin use and pemetrexed infusion will overlap because they are administered thirty minutes apart and that when this happens Dr. Reddy's product will mix with the saline solution due to the prehydration requirement. The resulting solution will contain pemetrexed molecules and sodium and tromethamine ions that disassociate from each other. Lilly explains that Dr. Reddy's product will be mixed with saline solution as it is being infused into a patient through the same intravenous line as the saline prehydration. The resulting solution will contain pemetrexed and sodium ions—that is pemetrexed disodium.

Dr. Reddy's responds that Lilly's theory of literal infringement would require healthcare providers to completely disregard its label instructions to use the Dr. Reddy's product with dextrose solution only. Lilly relies on the fact that the label does not explicitly instruct not to use saline and that a POSA would know that saline is suitable for use with pemetrexed drugs as Lilly's product has been safely administered with saline for over a decade. (Filing No. 146 at 15.) Dr. Reddy's label states that co-administration of Dr. Reddy's products with other diluents has not been studied and is therefore not recommended. Dr. Reddy's argues that Lilly's literal

infringement claim must prove that the Dr. Reddy's label instructs users to mix the Dr. Reddy's product with saline. Dr. Reddy's label also states that its product should not mix with anything except dextrose before it is infused. Dr. Reddy's also explains that even if healthcare providers mixed Dr. Reddy's pemetrexed ditromethamine with saline this would not be "administration of pemetrexed disodium" as required by Lilly's patent claims.

The claim construction issue has been resolved as a liquid administration of pemetrexed disodium. For purposes of summary judgment, the Court must credit Lilly's literal infringement theory that cisplatin's requirement and established practice of saline prehydration would overlap with the pemetrexed infusion and the two would mix via healthcare providers administering both through the same intravenous line. Furthermore, because saline contains sodium ions that this would result in infringement when Dr. Reddy's pemetrexed ditromethamine product is mixed with the saline resulting in a liquid administration of the pemetrexed disodium solution. Based on the foregoing, viewing the facts in a light favorable to Lilly, there are disputed issues of material fact as to whether every limitation of the asserted claim is literally met by the allegedly infringing device. Thus, Dr. Reddy's Motion for Summary Judgment of Noninfringement (Filing No. 132) is **denied** as to literal infringement.

C. Doctrine of Equivalents

"The doctrine of equivalents extends the right to exclude beyond the literal scope of the claims." *Johnson*, 285 F.3d at 1053. "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002). The doctrine of equivalents is restricted by the "all limitations" rule

and the prosecution history estoppel rule by limiting the range of equivalents when claims have been narrowed. *See Pozen Inc. v. Par Pharmaceutical, Inc.*, 696 F.3d 1151, 1167. Dr. Reddy's argues that Lilly's doctrine of equivalents infringement claim is foreclosed by prosecution history estoppel, the disclosure dedication rule, and doctrine of vitiation. The Court will address each of these threshold arguments in turn.

1. Prosecution History Estoppel

Dr. Reddy's argues that prosecution history estoppel bars Lilly's doctrine of equivalents claim at the threshold as a matter of law. (Filing No. 182 at 12.) It is undisputed that Lilly narrowed its broader antifolates claim to pemetrexed disodium during prosecution to avoid Arsenyan prior art. It is also undisputed that Dr. Reddy's product would fall within the scope of the original antifolates claim. Under *Festo*, Lilly's narrowing amendment triggers a presumption of surrender that Lilly must rebut to sustain its doctrine of equivalents claim. *Festo*, 535 U.S. at 725. *Festo* held three exceptions to defeat prosecution history estoppel:

> The equivalent may have been unforeseeable at the time of the application; the rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question; or there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question. In those cases the patentee can overcome the presumption that prosecution history estoppel bars finding an equivalence.

Id. at 740-41. Lilly argues that the tangential exception applies here, in that the different salt forms of pemetrexed used bear no more than a tangential relationship to the rationale for the underlying amendment. (Filing No. 146 at 23.) Lilly concedes that the amendment was to overcome a rejection in view of Arsenyan, however it explains that Arsenyan is a prior art article about the

administration of a compound called methotrexate, also an antifolate but distinguishable from pemetrexed.

Dr. Reddy's incorrectly reads *Festo* to hold that the rationale for the amendment must be both unforeseeable and tangential, but explains that even if tangential is an independent basis, Lilly is nevertheless precluded from asserting doctrine of equivalents because Lilly's narrowing amendment went to the identity of a particular type of antifolate—pemetrexed disodium. (Filing No. 167 at 6.) Dr. Reddy's goes on to cite Lilly's prosecution of the European equivalent of the '209 Patent where Lilly claimed pemetrexed broadly and used a dependent claim to claim the salt form: pemetrexed disodium. (Filing No. 182 at 16U.) This argument goes to foreseeability that Lilly allegedly knew how to draft a broad pemetrexed claim that was not narrowly limited to disodium salt.

Lilly argues that for the tangential exception "it makes no difference whether Lilly 'limited the scope of drugs in the claimed method' in a way that turned out to exclude the accused pemetrexed ditromethamine." Because pemetrexed, the active drug substance, actually treats the cancer patient, and pemetrexed disodium and pemetrexed ditromethamine are very similar, this exception necessarily presents a battle of the experts issue. In fact, it is undisputed that a POSA would understand that pemetrexed is the active antifolate (or drug) in both products.

In *Regents of University of Cal. v. Dakocytomation Cal. Inc.*, the Federal Circuit held that a patentee's narrowing amendment that centered on a method of blocking to avoid prior art that did *not* involve blocking was tangential to the particular nucleic acid used to accomplish the blocking. 517 F. 3d 1364, 1378 (Fed. Cir. 2008). The patent at issue in that case claimed "blocking nucleic acid" which was construed by the district court to involve human DNA, whereas the

accused product used synthetic (not human) nucleic acids referred to as peptide nucleic acids. *Id.* The district court granted summary judgment of noninfringement to the maker of the accused products because it held that the patentees had narrowed the scope of "blocking nucleic acid" during prosecution which barred the patentees from asserting the peptide nucleic acid equivalent. *Id.* The Federal Circuit reversed holding "[t]he prosecution history therefore reveals that in narrowing the claim to overcome the prior art rejections, the focus of the patentees' arguments centered on the method of blocking—not on the particular type of nucleic acid that could be used for blocking." *Id.* Thus, the Federal Circuit found the narrowing amendment was tangential.

The present case is similar to the distinction presented in *Regents*. The '209 Patent's specification describes a method for pemetrexed disodium treatment. Lilly's expert opined that a POSA would understand pemetrexed is the active antifolate that inhibits the enzymes at issue and treats the cancer. Dr. Reddy's argues that the salt form used in the patent goes to the identity of the antifolate that Lilly sought to claim and is thus barred from claiming pemetrexed as a class under prosecution history estoppel.

The prosecution history reveals that the Patent Office rejected various Lilly claims due to the prior art Arsenyan.

> Claims 2, 7, 10, 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Arsenyan et al. (Abstract; *Onkol., Nauchn.,* (1978) 12(10); 49-54. Arsenyan et al. teaches a method of pretreating mammals (mice) with various types of cancer with methylcobalamin (a vitamin B12 derivative which reduces methylmalonic acid) then administering methotrexate (an antifolate), and reports increased tumor inhibition and survival with methylcobalamin treatment.

(Filing No. 133-1 at 115.) The Arsenyan prior art rejection also served as the basis for an obviousness rejection. (Filing No. 133-1 at 117.) The prior art rejections thus went to

patentability. The Patent Office's communications do not refer to pemetrexed broadly, but also refer to pemetrexed disodium in combination with the pretreatment regimen as not being anticipated by the prior art. This is probably because ALIMTA® is sometimes used interchangeably with pemetrexed disodium during Lilly's patent prosecution. (*See* Filing No. 133-1 at 136.) At one point the Patent Office rejected Lilly's use of the trade name ALIMTA® in its claims as being vague and indefinite language, and Lilly responded with substituting pemetrexed disodium for ALIMTA®. (Filing No. 133-1 at 115.)

To overcome the prior art rejection, Lilly argued that the invention was new and nonobvious because it used the pretreatment regimen in combination with administration of pemetrexed disodium to treat the cancer and reduce the toxicities associated with pemetrexed disodium administration. (Filing No. 133-1 at 127.) The narrowing amendment (from antifolates as a class to pemetrexed disodium) was only tangential to the accused pemetrexed equivalent—pemetrexed ditromethamine. Thus, Lilly has met its burden of showing that it did not surrender the equivalent in question because the choice of pemetrexed salt is tangential to the reasons for the amendment and summary judgment is precluded on this issue.

2. Disclosure Dedication Doctrine

Dr. Reddy's argues that Lilly's equivalents claim is also barred by the disclosure dedication rule. "[W]hen a patent drafter discloses but declines to claim subject matter. . .this action dedicates that unclaimed subject matter to the public." *Johnson,* 285 F. 3d at 1054. "[T]he public notice function of patents suggests that before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation." *Pfizer,* 429 F. 3d 1379.

It is undisputed that the '209 Patent's specifications do not expressly disclose pemetrexed ditromethamine. Dr. Reddy's bases its disclosure dedication argument on the fact that the '209 Patent referenced another patent, Akimoto, and the pemetrexed salt derivatives described by Akimoto would include pemetrexed ditromethamine. (Filing No. 167 at 13.) Lilly responds that "[t]he Federal Circuit has recognized the possibility of using the specification of a different patent only where it was expressly incorporated by reference." (Filing No. 146 at 28.)

The disclosure dedication rule has limitations. Generic references in a written specification do not necessarily dedicate all members of a particular genus to the public. *SanDisk Corp. v. Kingston Technology Co., Inc.*, 695 F.3d 1348, 1363 (Fed. Cir. 2012).

> Rather, the 'disclosure must be of such specificity that one of ordinary skill in the art could identify the subject matter that had been disclosed and not claimed.' Additionally, in *Pfizer Inc. v. Teva Pharmaceuticals, USA, Inc.*, 429 F.3d 1364 (Fed. Cir. 2005), this court further clarified that 'before unclaimed subject matter is deemed to have been dedicated to the public, that unclaimed subject matter must have been identified by the patentee as an alternative to a claim limitation.'

Id. (citations omitted). There are two issues with Dr. Reddy's disclosure dedication argument. First, the '209 Patent did not expressly incorporate Akimoto by reference. Rather, the '209 Patent cites that preferred examples of antifolates can be found in the derivatives described by Akimoto. (Filing No. 1-1 at 5.) Dr. Reddy's argues that if a POSA went looking in Akimoto that the POSA would find pemetrexed and other substituted ammonium salts. To this second issue, Lilly responds that its experts will testify that Akimoto discloses a broader genus which would balloon out to over 200,000 compounds. The Court agrees that because of this large generic genus, no POSA would understand Akimoto to specifically disclose pemetrexed, tromethamine, or pemetrexed ditromethamine from the broader genus of compounds that Akimoto discloses unless they knew

to go looking for it. The disclosure dedication issue presented in this case hinges on what a POSA would recognize as unclaimed subject matter disclosed in the '209 Patent specification and if Akimoto's disclosures in combination would disclose pemetrexed ditromethamine. The Akimoto reference does not satisfy the disclosure dedication rule's requirements of a specific identification that amounted to a disclosure of an alternative to a claim limitation. Because pemetrexed ditromethamine was not disclosed and identified with specificity, the disclosure dedication rule does not prevent Lilly from pursuing a doctrine of equivalents infringement theory nor dedicated it to the public.

3. Doctrine of Vitiation

"[I]n cases where the patentee's theory of equivalents would 'entirely vitiate a particular claim element, partial or complete summary judgment should be rendered by the court.'" *Sage Products, Inc., v. Devon Industries, Inc.,* 126 F.3d 1420, 1429 (Fed. Cir. 1997) (citation omitted). The doctrine of vitiation or the "all elements" rule forecloses a patentee's resort to the doctrine of equivalents when the facts or theories presented in a case would completely read a limitation out of a claim because "all elements" of a claim must be present in an accused product for there to be infringement. *See Depuy Spine,* 469 F.3d at 1017.

Dr. Reddy's argues that the amended (and limiting) term pemetrexed disodium would be read out of the claim and restored with the rejected term "antifolates" under Lilly's theory of equivalents as articulated in its expert reports. Lilly responds that its theory on the scope of equivalents does not encompass all antifolates; rather, Lilly poses the function-way-result test to prove that the two products are equivalent in the context of the claimed treatment claims because they both involve pemetrexed treatment that results in a chemotherapy effect. The dispute between

the parties on this issue includes a discussion of Lilly's expert, Dr. Bruce A. Chabner's ("Dr. Chabner"), report and deposition. Dr. Reddy's contends that Dr. Chabner raises new theories on defining the function-way-result test in his deposition which were not raised in his expert report that are inadmissible at trial and at the summary judgment stage. (Filing No. 167 at 16). Specifically, Dr. Reddy's argues that Dr. Chabner changed his "way" analysis from "inhibition of [] folate-dependent enzymes" to "inhibition of *particular* folate-dependent enzymes." *Id*. at 16. (emphasis added). Previously, the Court ruled that Dr. Chabner's report and deposition were admissible when the Court sustained Lilly's objection to the Magistrate Judge's striking portions of this evidence as well as Lilly's literal infringement theory. (Filing No. 154.) Additionally, the factual record on the distinction between pemetrexed disodium and pemetrexed ditromethamine precludes summary judgment as it presents a clear battle of the experts issue. The different salt form that is used between the two products goes directly to the heart of Lilly's doctrine of equivalents claim and the limitation is thus not entirely vitiated by the substitution. Because there are factual issues precluding summary judgment on the doctrine of equivalents and Lilly has met its burden in clearing the threshold issues raised by Dr. Reddy's, summary judgment is not warranted.

D. Indirect Infringement

Direct infringement occurs when one party makes, uses, offers to sell, sells, or imports each element of a patented invention. 35 U.S.C. § 271(a). Because Dr. Reddy's does not provide care to patients the direct infringement is attributed to the healthcare providers. A party can be held liable for indirect infringement by actively inducing or contributing to direct infringement by others. 35 U.S.C. § 271(b), (c).

The Court will address liability for inducement of infringement first. "Liability for inducement of infringement is predicated on a finding of direct infringement by a third party." *Eli Lilly and Co. v. Teva Parenteral Medicines, Inc.,* 126 F. Supp. 3d 1037, 1041 (S.D. Ind. 2015) (citing *Limelight Networks v. Akamai Technologies Inc.,* 134 S.Ct. 2111, 2117 (2014)). "Inducement requires that the alleged infringer knowingly induced infringement and possessed a specific intent to encourage another's infringement." *AstraZeneca LP v. Apotex, Inc.,* 633 F.3d 1042, 1056 (Fed. Cir. 2010). Courts have inferred intent to induce infringement based on the contents of labels. *Id.* (holding circumstantial evidence may suffice to prove specific intent to induce infringement). "The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [] affirmative intent to induce infringement." *AstraZeneca,* 633 F.3d at 1060. Similarly, labels may also form the basis to infer intent under contributory infringement when they instruct users to perform a patented method. *See Eli Lilly & Co. v. Actavis Elizabeth LLC,* 435 F. App'x 917, 926 (Fed. Cir. 2011).

Liability for contributory infringement under 35 U.S.C. § 271(c) can be avoided if the product is a "staple article or commodity of commerce suitable for substantial noninfringing use." "One who makes and sells articles which are only adapted to be used in a patented combination will be presumed to intend the natural consequences of his acts; he will be presumed to intend that they shall be used in the combination of the patent." *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.* 545 U.S. 913, 932 (2005).

Reviewing the record in a light most favorable to Lilly, Lilly has shown that Dr. Reddy's product will result in induced or contributory infringement. With regards to the literal

infringement theory and cisplatin use, Lilly argues that standard practice would require healthcare providers to use saline solution with cisplatin which would then result in a solution containing pemetrexed and disodium ions—*i.e.* pemetrexed disodium. Specific, knowing intent is required for inducement and contributory infringement. Nevertheless, Lilly has shown there are disputed issues of material fact on whether Dr. Reddy's label instructs an infringing use under either literal infringement or the doctrine of equivalents to infer intent and knowledge necessary for either form of indirect infringement. "Even where a proposed label does not explicitly track the language of a claimed method, a package insert containing directives that will 'inevitably lead some consumers to practice the claimed method' provides sufficient evidence for a finding of specific intent." *Sanofi v. Glenmark Pharmaceuticals Inc., USA,* 204 F. Supp. 3d 665, 673-74 (D. Ct. Del.) (quoting *AstraZeneca,* 633 F. 3d at 1060). In a Hatch-Waxman case such as this, infringement "is focused on the product that is likely to be sold following FDA approval," including the relevant knowledge of the parties at the time the product is sold. *See Abbott Laboratories v. TorPharm, Inc.,* 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("This determination is based on consideration of all the relevant evidence, including the ANDA filing, other materials submitted by the accused infringer to the FDA, and other evidence provided by the parties."). Viewing the facts in the light most favorable to Lilly, it has shown that Dr. Reddy's label will instruct users to perform the patented method by inducing or contributing to infringement and that Dr. Reddy's had the requisite intent and knowledge that its label would cause such infringement. Thus, summary judgment is precluded.

IV. CONCLUSION

There are genuine disputes of material fact with respect to the claims before the Court. For the reasons stated above, Dr. Reddy's Motion for Summary Judgment (Filing No. 132) is **DENIED**. Lilly's literal infringement and doctrine of equivalents claims remain pending for trial.

SO ORDERED.

Date: 12/14/2017

TANYA WALTON PRATT, JUDGE
United States District Court
Southern District of Indiana

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EXHIBIT A



(12) **United States Patent**
Niyikiza

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(54) **ANTIFOLATE COMBINATION THERAPIES**

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(60) Provisional application No. 60/215,310, filed on Jun. 30, 2000, provisional application No. 60/235,859, filed on Sep. 27, 2000, provisional application No. 60/284,448, filed on Apr. 18, 2001.

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(58) **Field of Classification Search** 514/52, 514/77, 249, 251, 265.1

See application file for complete search history.

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(57) **ABSTRACT**

A method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

22 Claims, No Drawings

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ANTIFOLATE COMBINATION THERAPIES

This application is a divisional of application Ser. No. 11/288,807, filed 29 Nov., 2005 now abandoned, which is a divisional of application Ser. No. 10/297,821 filed 12 May, 2002, now U.S. Pat. No. 7,053,065, which claims priority under 35 USC 371, for PCT/US01/14860, filed 15 Jun., 2001, which claims the priority of U.S. provisional applications No. 60/215,310, filed 30 Jun., 2000, No. 60/235,859, filed 27 Sep., 2000, and No. 60/284,448, filed 18 Apr., 2001.

Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (see, generally, *Antifolate Drugs in Cancer Therapy*, edited by Jackman, Ann L., Humana Press, Totowa, N.J., 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (*Antifolate*, pg 197.)

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer. (Bonnadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: Ten year results. JAMA 1995;273(7):542-547; Bonnadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med 1995; 332(14):901-906; and Hong W K, Schaefer S, Issell B, et al. A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. Cancer 1983; 52:206-210.) Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), by competing with reduced folates for binding sites of these enzymes. (Shih C, Habeck L L, Mendelsohn L G, Chen V J, Schultz R M. Multiple folate enzyme inhibition: Mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Advan Enzyme Regul, 1998; 38:135-152 and Shih C, Chen V J, Gossett L S, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997; 57:1116-1123.) Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex®. An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristic is Methotrexate®. An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta®, Eli Lilly and Company, Indianapolis, Ind.) has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally antifolates as a class are associated with sporadic severe mylosuppression with gastrointestinal toxicity which, though infrequent, carries a high risk of mortality. The

inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed. (Jackman A L, Calvert A H Folate-Based Thymidylate Synthase Inhibitors as Anticancer Drugs. Ann Oncol 1995; 6(9):871-881; Laohavinij S, Wedge S R, Lind M J, et al. A phase I clinical study of the antipurine antifolate Lometrexol (DDATHF) given with oral folic acid. Invest New Drugs 1996; 14:325-335; and Maughan T S, James R D, Kerr D, et al., on behalf of the British MRC Colorectal Cancer Working Party. Preliminary results of a multicenter randomized trial comparing 3 chemotherapy regimens (deGramont, Lokich, and raltitrexed) in metastatic colorectal cancer. Proc ASCO 1999; 18:Abst 1007.) Initially, folic acid was used as a treatment for toxicities associated with GARFTI see, e.g. U.S. Pat. No. 5,217,974. Folic acid has been shown to lower homocysteine levels (see e.g. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ 1998; 316:894-898 and Naurath H J, Joosten E, Riezler R, Stabler S P, Allen R H, Lindenbaum J. Effects of vitamin B 12, folate and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. Lancet 1995; 346:85-89), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors, see e.g. U.S. Pat. No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent. We have discovered that increased levels of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin B12, reduces mortality and nonhematologic events, such as skin rashes and fatigue events previously associated with the antifolate drugs.

Additionally, we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

The present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

Furthermore, the present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent and a FBP binding agent. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent, alone or in combination with a FBP binding agent, in the preparation of a medicament useful in lowering the mammalian toxicity of an antifolate. A preferred FBP binding agent is folic acid.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent.

Furthermore, the present invention relates to the use of a methylmalonic acid lowering agent in the manufacture of a medicament for use in a method of inhibiting tumor growth in mammals, which method comprises administering said methylmalonic acid lowering agent in combination with an antifolate.

Furthermore, the present invention relates to a product containing a methylmalonic acid lowering agent, an antifolate and optionally a FBP binding agent as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth.

The current invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of the said antifolate drug.

The term "inhibit" as it relates to antifolate drugs refers to prohibiting, alleviating, ameliorating, halting, restraining, slowing or reversing the progression of, or reducing tumor growth.

As used herein, the term "effective amount" refers to an amount of a compound or drug, which is capable of performing the intended result. For example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount which is required to reduce tumor growth.

As used herein, the term "toxicity" refers to a toxic event associated with the administration on an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, and anemia. For further explanation of the types of toxicity experienced by patients receiving antifolates, see, generally, *Antifolate Drugs in Cancer Therapy*. Preferably, toxicity refers to toxic death, fatigue, neutropenia, thrombopenia, and mucositis.

As used herein, the term "nonhematologic event" refers to the occurrence of skin rash or fatigue due to the administration of an antifolate.

As used herein, the term "in combination with" refers to the administration of the methylmalonic acid lowering agent, the antifolate drug, and optionally the folic acid; in any order such that sufficient levels of methylmalonic acid lowering agent and optionally folic acid are present to reduce the toxicity of an antifolate in a mammal. The administration of the compounds maybe simultaneous as a single composition or as two separate compositions or can be administered sequentially as separate compositions such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered. The antifolate drug may be administered to the mammal first, followed by treatment with the methylmalonic acid lowering agent. Alternatively, the mammal may be administered the antifolate drug simultaneously with the methylmalonic acid lowering agent. Preferably, the mammal is pretreated with the methylmalonic acid lowering agent and then treated with the antifolate. If folic acid is to be administered in addition to the methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is pretreated with the methylmalonic acid, and then treated with folic acid, followed by treatment with the antifolate compound.

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include Tomudex®, as manufactured by Zeneca; Methotrexate®, as manufactured by Lederle; Lometrexol®, as manufactured by Tularik; pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, 4,902,796, 4,871,743, and 4,882,334; derivatives described by Akimoto in U.S. Pat. No. 4,997,838; thymidylate synthase inhibitors as found in EPO application 239,362; and most preferred, Pemetrexed Disodium (ALIMTA), as manufactured by Eli Lilly & Co.

The terms "methylmalonic acid" and "MMA" refer to a structural isomer of succinic acid present in minute amounts in healthy human urine.

The term "methylmalonic acid lowering agent" refers to a substrate, which lowers the concentration of methylmalonic acid in a mammal. A preferred example of such a substrate is vitamin B12. For methods of determining methylmalonic acid and substrates therefore, see, e.g., Matchar D B, Feussner J R, Millington D S, et al. Isotope dilution assay for urinary methylmalonic acid in the diagnosis of vitamin B12 deficiency. A prospective clinical evaluation. Ann Intern Med 1987; 106: 707-710; Norman E J, Morrison J A. Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry. Am J Med 1993; 94: 589-594; Norman E J. Gas Chromatography mass spectrometry screening of urinary methylmalonic acid: early detection of vitamin B12 (cobalamin) deficiency to prevent permanent neurologic disability. GC/MS News 1984; 12:120-129; Martin D C, Francis J, Protetch J, Huff F J. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. JAGS 1992; 40: 168-172; Norman E J, Cronin C. Cobalamin deficiency. Neurol 1996; 47: 310-311; Rasmussen K, Moelby I, Jensen M K. Studies on methylmalonic acid

in humans; Savage D G, Lindenbaum J, Stabler S P, Allen R H. Sensitivity of methylmalonic acid and total homocysteine determination for diagnosing cobalamin and folate deficiency. Am J Med 1994; 96: 239-246.

The term "vitamin B12" refers to vitamin B12 and its pharmaceutical derivatives, such as hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin. Preferably the term refers to vitamin B12, cobalamin, and chlorocobalamin.

The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, such as a sustained release formulation, as an aqueous solution added to drinking water, or as an aqueous parenteral formulation. Preferably the methylmalonic acid lowering agent is administered as an intramuscular injection formulation. Such formulations are known in the art and are commercially available.

The skilled artisan will appreciate that the methylmalonic lowering agents are effective over a wide dosage range. For example, when cobalamin is used as the methylmalonic lowering agent, the dosage of cobalamin may fall within the range of about 0.2 μg to about 3000 μg of cobalamin from once daily for a month to once every nine weeks for a year. Preferably, cobalamin will be dosed as an intramuscular injection of about 500 μg to about 1500 μg administered from about every 24 hours to about every 1680 hours. Preferably, it is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to administration of the antifolate and repeated from about every 24 hours to about every 1680 hours, regardless of when treatment with the antifolate is started and continued until the administration of the antifolate is discontinued. Most preferred is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to the first administration of the antifolate and repeated every 6 to 12 weeks, preferably about every 9 weeks, and continued until the discontinuation of the antifolate administrations. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

The term "FBP binding agent" as used herein refers to a folic binding protein binding agent which includes folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof. This latter compound is the (6R)-isomer of leucovorin as disclosed in J. Am. Chem. Soc., 74, 4215 (1952). Both of the tetrahydrofolic acid compounds are in the unnatural configuration at the 6-position. They are 10-20 fold more efficient in binding the folate binding protein compared with their respective (6S)-isomer, see Ratnam, et. al., Folate and Antifolate Transport in Mammalian Cells Symposium, Mar. 21-22, 1991, Bethesda, Md. These compounds are usually prepared as a mixture with their natural form (6S) of diastereomers by non-stereoselective reduction from the corresponding dehydro precursors followed by separation through chromatographic or enzymatic techniques. See e.g. PCT Patent Application Publication WO 880844 (also Derwent Abstract 88-368464/51) and Canadian Patent 1093554. See, e.g. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (2000), 8 Folate, pp. 196-305.

"Physiologically-available salt" refers to potassium, sodium, lithium, magnesium, or preferably a calcium salt of the FBP binding agent. "Physiologically-available . . . ester" refers to esters which are easily hydrolyzed upon administration to a mammal to provide the corresponding FBP binding agent free acid, such as C_1-C_4 alkyl esters, mixed anhydrides, and the like.

The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement, namely as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e.g., an intravenous formulation, or the like.

The FBP binding agent is usually administered to the subject mammal prior to treatment with the antifolate. Pretreatment with the suitable amount of FBP binding agent from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment.

In the especially preferred embodiment of this invention, about 0.1 mg to about 30 mg, most preferably about 0.3 mg to about 5 mg, of folic acid is administered orally to a mammal about 1 to 3 weeks post administration of the methylmalonic acid lowering agent and about 1 to about 24 hours prior to the parenteral administration of the amount of an antifolate. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

In general, the term "pharmaceutical" when used as an adjective means substantially non-toxic to living organisms.

Methods

To assess the effect of a methylmalonic acid lowering agent, alone or in combination with folic acid on the antitumor efficacy of an antifolate in a human tumor xenograft model, female nude mice bearing human MX-1 breast carcinoma were treated with ALIMTA alone or along with superphysiologic doses of folic acid or vitamin B12 (cobalamin).

The animals were maintained on sterilized standard lab chow ad libitum and sterilized water ad libitum. The human MX-1 tumor cells (5×10^6) obtained from donor tumors were implanted subcutaneously in a thigh of female nude mice 8- to 10-weeks old. Beginning on day 7 post tumor cell implanta-

tion, the animals were treated with ALIMTA (100 mg/kg or 150 mg/kg) once daily on days 7 through 11 and 14 through 18 by intraperitoneal injection alone or along with folic acid (6 mg/kg or 60 mg/kg) and/or vitamin B12 (165 mg/kg) by intraperitoneal injection on the same schedule.

Tumor response was monitored by tumor volume measurements twice weekly over the course of the experiment. Toxicity was monitored by body weight measurements made at the same time as the tumor volume measurements. Tumor growth delay was the difference in days for the treated and the controls tumors to reach 1000 mm^3.

The human MX-1 breast carcinoma xenograft was responsive to treatment with ALIMTA with doses of 100 mg/kg and 150 mg/kg producing tumor growth delays of 17 days and 21 days, respectively. Folic acid was administered to the animals alone at two doses 6 mg/kg and 60 mg/kg on the same schedule as ALIMTA and produced tumor growth delays of 7 days and 12 days, respectively. Vitamin B12 administered alone at a dose of 165 mg/kg resulted in a tumor growth delay of 12 days.

Combinations of ALIMTA at each of the two doses were administered along with each of the vitamins as simultaneous combination regimens. Administration of folic acid (6 mg/kg) along with ALIMTA did not alter the tumor growth delay produced from that obtained with ALIMTA alone. The addition of folic acid at the higher dose (60 mg/kg) along with each dose of ALIMTA resulted in small increases in tumor growth delay to 22 days and 23 days at the ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively. The tumor growth delays with ALIMTA and vitamin B12 (165 mg/kg) treatment were 22 days and 24 days at ALIMTA doses of 100 mg/kg and 150 mg/kg, respectively.

Body weight was used as a general measure of toxicity for each of the treatment regimens. The body weight loss pattern reflected the treatment regimens with weight decrease during the treatment times of days 7 through 11 and 14 through 18 with some weight recovery during the intervening two days. The weight loss due to ALITMA was dose dependent but overall minor (3%). Folic acid alone at either 6 mg/kg or 60 mg/kg did not cause weight loss, in fact folic acid treated animals maintained weight and gained weight over the course of the experiment better than the control animals. The animals treated with ALIMTA (100 mg/kg) and folic acid (60 mg/kg) gained weight (about 20%) over the course of the experiment.

Administration of vitamin B12 did not prevent weight gain in the animals over the time course of the experiment. The animals treated with ALIMTA (100 mg/kg) along with vitamin B12 gained weight while those treated with ALIMTA (150 mg/kg) along with vitamin B 12 maintained weight over the course of the experiment.

In conclusion, administration of super-physiologic but non-toxic doses of the vitamins, folic acid and vitamin B12, did not alter the antitumor activity of ALIMTA in the human MX-1 breast carcinoma xenograft tumor in nude mice and did not increase the toxicity of ALIMTA as determined by body weight measurements of the animals.

The effect of vitamin B12, alone or in combination with folic acid, on antifolates can be demonstrated in standard tests commonly utilized to determine the antitumor activity and toxic effects of the antifolates themselves. In one such test, mice are inoculated with the C3H strain of mammary adenocarcinoma by inserting a 2 mm by 2 mm section of tumor into the axillary region of the mice by trocar. The timing of administering the methylmalonic acid lowering agent, alone or in combination with the folic acid, and the antifolate may be varied. Ten animals are used at each dosage level. Antitumor activity is assessed on day ten (when day one is first dosage of antifolate) by measuring the length and width of the tumor growth using vernier calipers, and the activity is expressed as a percent inhibition of tumor growth.

When the antifolate is administered to infected mice which are maintained on a diet totally free of vitamin B12 and optionally folic acid for two weeks prior to and during treatment, it exhibits moderated antitumor activity at very low doses, but also causes severe toxicity at a very low dose (measured as death of mice).

A test group of mice are maintained on a vitamin B12 and optionally folic acid free diet for two weeks before treatment. Vitamin B12 and optionally folic acid is then administered during the treatment by intramuscular injection of 0.0003% vitamin B12 (weight/volume) and optionally providing the animals drinking water containing 0.0003% folic acid (weight/volume). This concentration translates to about 1.75 mg of vitamin B12 and optionally folic acid per square meter of body surface per day. As the foregoing results indicate, addition of the indicated level of vitamin B12 to the diet of a subject receiving an antifolate results in excellent antitumor activity at low doses, with little or no toxic effects.

The foregoing tests establish that for tumor bearing mice maintained on a vitamin B12 and optionally folic acid free diet prior to and during treatment with an antifolate, the toxicity of the antifolate is very large, with 1 mg/kg/day being lethal to the majority of the mice, and lower antitumor activity is observed at non-toxic drug doses. Very low doses of vitamin B12 partially reverses drug toxicity and improved antitumor activity. Larger doses of vitamin B12 reduce antifolate toxicity even more significantly. Pretreatment of the mouse with vitamin B12 and then administering folic acid prior to administering the antifolate demonstrates a striking reduction in toxicity, almost eliminating the antifolate toxicity completely. Thus, the use of vitamin B12 in combination with an antifolate reduces drug toxicity without adversely affecting antitumor activity, and the use of vitamin B12 in conjunction with folic acid synergistically reduces drug toxicity.

In a typical clinical evaluation involving cancer patients, all of whom have histologically or cytologically confirmed diagnosis of cancer, an antifolate is administered in combination with vitamin B12. Vitamin B12 is administered as a 1000 μg intramuscular injection 1-3 weeks prior to treatment with the antifolate, and 1000 μg intramuscular injection of vitamin B12 is made approximately every 9 weeks until the patient discontinues from therapy. The antifolate is administered in four doses over a two week period by rapid intravenous injection, followed by two weeks of non-therapy. Dosing is made on days 1, 4, 8 and 11 of any two week period. Patients will have an initial course of therapy at a dose of 5 mg/m^2/dose, and depending upon the toxic effects observed in the initial course, their subsequent courses may be at the same dose, or may be escalated to 6 mg/m^2, or may be attenuated to 4 mg/m^2.

In preparation for the foregoing clinical study, pilot studies in humans have established that vitamin B12 given to patients receiving Alimta has effected reduced side effects due to the Alimta. One to two weeks prior to administration of ALIMTA urine is collected and blood is drawn from a human subject; and vitamin metabolite levels, methylmalonic acid and homocysteine, are determined. Homocysteine levels are determined in blood by a fluorescent polarization immunoassay kit manufactured by Abbot Laboratories. Methylmalonic acid levels are determined by urine levels using a 24 hour urine collection kit available from Biolab Medical Unit (a United Kingdom company). Additionally urine and blood may be collected one week prior to administration of

ALIMTA (after at least 5 days of folic acid supplementation and at least 1 week vitamin B12 supplementation), and up to 4 days prior to every cycle.

Method of Administration and Dosing Procedures:

1. Folic Acid:

Folic acid will be supplied as one of the following options, with preference in order from option #1 to option #3:

1. 350-600 μg folic acid.
2. A multivitamin containing folic acid in the range of 350 μg to 600 μg is acceptable if option #1 is not available.
3. A dose of folic acid between 350 μg and 1000 μg is acceptable if neither option #1 or option # 2 is available.

For purposes of this study, patients should take oral folic acid daily beginning approximately 1 to 3 weeks before treatment with ALIMTA plus cisplatin or cisplatin alone and continuing daily until discontinuation from study therapy.

2. Vitamin B12

Vitamin B12 will be obtained and administered as a 1000 μg intramuscular injection. A vitamin B12 injection must be administered approximately 1 to 3 weeks before treatment with ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Folic acid supplementation, 350-600 μg or equivalent should be taken orally daily beginning approximately 1 to 3 weeks prior to the first dose of MTA plus cisplatin and continue daily until the patient discontinues from study therapy. A vitamin B12 injection, 1000 μg, must be given intramuscularly approximately 1 to 3 weeks prior to the first dose of ALIMTA and should be repeated approximately every 9 weeks until the patient discontinues from study therapy.

Compare presupplementation homocysteine and methylmalonic acid levels to a) the level immediately prior to the initial dose of study drug, and b) to the level immediately prior to the second dose of study drug (i.e., after a full cycle of supplementation), and compare the prevalence of specific toxicities experienced in up to the first seven cycles of therapy in patients who have been supplemented from baseline to the prevalence seen in the earlier patients (n=246) who were not supplemented (Farber et al.)

Toxicity may be compared in specific patients in non-supplemented cycles versus supplemented cycles (cross-over patients).

The data to be compared are:

1) Patient numbers and baseline demographic data for those supplemented from baseline.
2) Homocysteine and methylmalonic acid levels, levels at baseline, prior to first dose, prior to second dose, and prior to each therapy cycle depending of the type of cancer under study.
3) Grade 3 and 4 hematologic toxicity in these fully supplemented patients.
4) Grade 3 and 4 nonhematologic toxicity in these fully supplemented patients.

The grading of toxicities in chemotherapuetic clinical trials is well known to a person of skill in the art. Examples of fatigue and skin rash grading are provided below.

Fatigue Grading—

Neuromotor

Grade 0 none or no change

Grade 1 subjective weakness; no objective findings

Grade 2 mild objective weakness without significant impairment of function

Grade 3 objective weakness with impairment of function

Grade 4 paralysis

Rash Grading—

Skin

Grade 0 none or no change

Grade 1 scattered macular or papular eruption or erythema that is asymptomatic

Grade 2 scattered macular or papular eruption or erythema with pruritus or other associated eruption symptoms

Grade 3 generalized symptomatic macular, papular, or vesicular eruption

Grade 4 exfoliative dermatitis or ulcerating dermatitis

The vitamins (both folic acid and B12) to be used in the following studies may be obtained from Zenith Gold Line, Centrum, Folvite, or in Canada Apo-Folic. Cyanocobalamin is used as the methylmalonic acid lowering agent in these studies.

Current and past clinical trials show a 4% drug-related death total, 50% grade 3/4 neutropenia, 7% grade 4 thrombocytopenia, and 10% grade 3/4 diarrheas and mucositis in patients administered ALIMTA and folic acid as described in U.S. Pat. No. 5,217,974. Vitamin B12 supplementation with ALIMTA has a moderate effect on drug related toxicity, lowering drug related deaths to 3% and severe toxicities by about 25%. The combination of vitamin B12 and folic acid with ALIMTA has lowered the drug related deaths to <1% in over 480 so treated. The combination of vitamin B12 and folic acid has lowered the drug related grade 3/4 toxic events, see Table 1.

TABLE 1

	Percent of occurrences prior to B12/folic acid treatment (N = 246)	Percent of occurrences post B12/folic acid treatment (N = 78)
Hematologic Toxicity/Non-Hematologic Toxicity	37%	6.4%
Neutropenia	32%	2.6%
Mucositis	5%	1.3%
Diarrhea	6%	2.6%
Neutropenia and Mucositis	3%	0%
Neutropenia and Diarrhea	3%	0%
Neutropenia and Infection	2%	0%

Additionally, sixty-two chemonaive patients requiring chemotherapeutic treatment were divided into two groups. Seventeen of these patients received ALIMTA, but did not receive vitamin B12 or folic acid, as described supra. The remaining patients received treatment with vitamin B12, folic acid, and ALIMTA, as described supra. Of patients who received the combination treatment, 8 out of 45 responded to the chemotherapy. Of patients who did not receive the combination treatment, but rather, received only treatment with ALIMTA, only 1 out of 17 patients responded.

I claim:

1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium, wherein

the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.

2. The method of claim **1**, wherein 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.

4. The method of claim **2**, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 μg.

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.

6. The method of claim **5** wherein the folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

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.

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.

9. The method of claim **8** wherein about 350 μg to about 1000 μg of folic acid is administered.

10. The method of claim **9** wherein 350 μg to 600 μg of folic acid is administered.

11. The method of claim **1** further comprising the administration of cisplatin to the patient.

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

a) administration of between about 350 μg and about 1000 μg of folic acid prior to the first administration of pemetrexed disodium;

b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first administration of pemetrexed disodium; and

c) administration of pemetrexed disodium.

13. The method of claim **12** further comprising the administration of cisplatin to the patient.

14. The method of claim **12**, wherein vitamin B12 is administered as an intramuscular injection of about 500 μg to about 1500 μg.

15. The method of claim **14**, wherein vitamin B12 is administered as an intramuscular injection of about 1000 μg.

16. The method of claim **15**, wherein between 0.3 mg to about 5 mg of folic acid is administered orally.

17. The method of claim **16** wherein about 350 μg to about 1000 μg of folic acid is administered.

18. The method of claim **17** wherein 350 μg to 600 μg of folic acid is administered.

19. The method of claim **18** wherein folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed disodium.

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.

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 administration of pemetrexed disodium is discontinued.

22. The method of claim **21** further comprising the administration of cisplatin to the patient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,772,209 B2
APPLICATION NO. : 11/776329
DATED : August 10, 2010
INVENTOR(S) : Clet Niyikiza

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Col. 2, Line 22, under Other Publications: Delete "Homocystein" and insert --Homocysteine--, therefor.

Title Page, Col. 2, Line 27, under other Publications: Delete "hydroxocobaltniin" and insert --hydroxocobalamin--, therefor.

Title Page, Col. 2, Line 28, under Other Publications: Delete "mce" and insert --mice--, therefor.

Title Page, Col. 2, Line 37, under Other Publications: Delete "2666" and insert --266--, therefor.

Column l, Line 5, Delete "12 May," and insert --5 Dec.--, therefor.

Column 10, Line 62, ln Claim l, delete "hydroxycobalamin," and insert --hydroxocobalamin,--, therefor.

Column 11, Line 4, ln Claim 4, delete "2," and insert --3,--, therefor.

Signed and Sealed this

Twenty-sixth Day of October, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF SERVICE

On October 9, 2018, the nonconfidential version of this brief was submitted to the Court by CM/ECF, and thereby served on all parties. The confidential version was filed with the Court by ECF, two copies were sent by FedEx to principal counsel for Plaintiff-Appellee Eli Lilly & Co. at the address below, and electronic courtesy copies were sent to counsel for Eli Lilly at aperlman@wc.com, gfomenkova@wc.com, dgrossman@wc.com, dkrinsky@wc.com, alemens@wc.com, and lmccloud@wc.com.

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This brief complies with the type-volume limitations of Fed. R. App. P. 32 and Fed. Cir. R. 32. According to the word-processing system used to prepare it, the brief contains 13,989 words.

/s/ John C. O'Quinn

CERTIFICATE OF COMPLIANCE WITH RULE 28(d)

This brief complies with the word limit of Fed. Cir. R. 28(d), and contains 15 words marked as confidential in the confidential version of this brief and redacted in the nonconfidential version.

/s/ John C. O'Quinn