Appeal No. 18-2128

In the United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,
Plaintiff-Appellee,

v.

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

Appeal from the United States District Court
for the Southern District of Indiana in No. 1:16-cv-308-TWP-MPB
(The Honorable Tanya Walton Pratt, J.)

BRIEF OF PLAINTIFF-APPELLEE ELI LILLY AND COMPANY

ADAM L. PERLMAN
DOV P. GROSSMAN
DAVID M. KRINSKY
GALINA I. FOMENKOVA
CHARLES L. MCCLOUD
ANDREW P. LEMENS
WILLIAMS & CONNOLLY LLP
725 Twelfth Street, N.W.
Washington, DC 20005
(202) 434-5000

JAMES P. LEEDS
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-1667

Attorneys for Plaintiff-Appellee

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, undersigned counsel for Plaintiff-Appellee certifies the following:

1. The full name of the party represented by me is Eli Lilly and Company.

2. Eli Lilly and Company has no parent corporation and no publicly held company owns 10 percent or more of its stock.

3. There are no additional parent corporations or publicly held companies that own 10 percent or more of the stock of the parties represented by me.

4. The names of all attorneys that appeared for the party now represented by me in the district court or are expected to appear in this court (and who have not or will not enter an appearance in this case) are: Bruce R. Genderson and Christopher T. Berg of Williams & Connolly LLP, Alec T. Swafford formerly of Williams & Connolly LLP, and Anne N. DePrez and Jan M. Carroll of Barnes & Thornburg LLP.

5. The title and number of any case known to me 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 are:

- *Neptune Generics, LLC v. Eli Lilly and Company*, Nos. 18-1257, -1258, -1288, -1290 (Fed. Cir.)
- *Eli Lilly and Company v. Hospira, Inc.*, No. 18-2126, -2127 (Fed. Cir.)
- *Eli Lilly and Company v. Nang Kuang Pharmaceutical Co.*, No. 1:14-cv-1647-TWP-MPB (S.D. Ind.)
- *Eli Lilly and Company v. Actavis LLC*, No. 1:17-cv-982-TWP-MPB (S.D. Ind.)

- *Eli Lilly and Company v. Amneal Pharmaceuticals LLC*, No. 1:17-cv-986-TWP-MPB (S.D. Ind.)
- *Eli Lilly and Company v. Jiangsu Hansoh Pharm. Group Co.*, No. 1:17-cv-2864-TWP-MPB (S.D. Ind.)
- *Eli Lilly and Company v. Apotex, Inc.*, No. 1:17-cv-2865-TWP-MPB (S.D. Ind.)
- *Eli Lilly and Company v. Eagle Pharmaceuticals, Inc.*, No. 17-cv-1293 (MSG) (D. Del.)
- *Eagle Pharmaceuticals, Inc. v. Eli Lilly and Company*, No. 18-cv-1121 (MSG) (D. Del.)

DECEMBER 3, 2018

/s/ *Adam L. Perlman*
ADAM L. PERLMAN

Attorney for Plaintiff-Appellee

TABLE OF CONTENTS

TABLE OF AUTHORITIES v
TABLE OF REFERENCES viii
STATEMENT OF RELATED CASES 1
STATEMENT OF THE ISSUES 2
STATEMENT OF THE CASE 3
I. BACKGROUND. 5
A. Antifolates and Pemetrexed. 5
B. The Person of Ordinary Skill. 6
C. Lilly's Claim Amendment During Prosecution. 7
D. Lilly's ALIMTA® 10
E. DRL's NDA Product. 11
II. THE DISTRICT COURT PROCEEDINGS. 11
SUMMARY OF ARGUMENT 16
STANDARD OF REVIEW 20
ARGUMENT 21
I. PROSECUTION HISTORY ESTOPPEL DOES NOT BAR LILLY FROM PURSUING THE DOCTRINE OF EQUIVALENTS. 21
A. The Reason for Lilly's Amendment Was Tangential to DRL's Proposed Pemetrexed Ditromethamine Equivalent. 22
1. The Tangentiality Exception Focuses on the Reason for an Amendment. 22
2. The District Court Correctly Concluded That the Reason for Lilly's Amendment Is Tangential to DRL's Proposed Equivalent. 24
3. This Court's Precedents Support the District Court's Conclusion. 26

B. DRL Misstates the Test for Tangentiality. 31

1. DRL Misconstrues the District Court's Analysis. 32

2. DRL's Focus on What the Patentee "Surrendered" Misconstrues the Tangentiality Analysis. 34

3. The Tangentiality Analysis Depends on the Reason for the Actual Amendment Lilly Made, Not the Reason It Did Not Make an Alternative, Broader Amendment. 43

4. The Tangentiality Exception Is Not Precluded Because Lilly's Rationale and DRL's Proposed Equivalent Involve the Same Claim Limitation.....47

II. THE DISCLOSURE-DEDICATION RULE DOES NOT BAR LILLY FROM PURSUING THE DOCTRINE OF EQUIVALENTS.....50

A. The Specification of the '209 Patent Does Not Expressly Disclose Pemetrexed Ditromethamine. 51

B. The Specification's Unincorporated Prior Art References Do Not Disclose Pemetrexed Ditromethamine. 54

C. Pemetrexed Ditromethamine Is Not Disclosed as an Alternative to Pemetrexed Disodium. 59

D. DRL's Other Asserted Errors Are Baseless. 60

III. THE DISTRICT COURT'S INFRINGEMENT FINDING WAS NOT CLEARLY ERRONEOUS. 62

CONCLUSION.....70

TABLE OF AUTHORITIES

FEDERAL CASES

Abbott Labs. v. Sandoz, Inc.,
566 F.3d 1282 (Fed. Cir. 2009) 52

Allergan, Inc. v. Sandoz Inc.,
796 F.3d 1293 (Fed. Cir. 2015) 21

Amgen Inc. v. Hoechst Marion Roussel Inc.,
457 F.3d 1293 (Fed. Cir. 2006) 49

Biagro W. Sales, Inc. v. Grow More, Inc.,
423 F.3d 1296 (Fed. Cir. 2005) 40, 48

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,
320 F.3d 1339 (Fed. Cir. 2003) 70

DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,
567 F.3d 1314 (Fed. Cir. 2009) 20

Eli Lilly and Company v. Teva Parenteral Meds., Inc.,
845 F.3d 1357 (Fed. Cir. 2017) 4, 6, 67

Eli Lilly and Company v. Teva Parenteral Meds., Inc.,
2014 WL 1350129 (S.D. Ind. Mar. 31, 2014) 6

Eli Lilly and Company v. Teva Parenteral Meds., Inc.,
2012 WL 2358102 (S.D. Ind. Jun. 20, 2012) 7

Felix v. American Honda Motor Company,
562 F.3d 1167 (Fed. Cir. 2009) 41-43

Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,
535 U.S. 722 (2002).....15, 22-23, 34, 46

Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.,
344 F.3d 1359 (Fed. Cir. 2003) (en banc) 20-21, 23-24, 26, 44-46, 49

Graver Tank & Mfg. Co. v. Linde Air Prods. Co.,
339 U.S. 605 (1950).....22

Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.,
523 F.3d 1304 (Fed. Cir. 2008) 20, 47, 48

Insituform Techs., Inc. v. CAT Contracting, Inc.,
385 F.3d 1360 (Fed. Cir. 2004) 26, 30-31, 37-38, 45

Integrated Tech. Corp. v. Rudolph Techs., Inc.,
734 F.3d 1352 (Fed. Cir. 2013) 36-37

Int'l Rectifier Corp. v. IXYS Corp.,
515 F.3d 1353 (Fed. Cir. 2008) 37

Intervet Inc. v. Merial Ltd.,
617 F.3d 1282 (Fed. Cir. 2010) 49

Johnson & Johnston Assocs. v. R.E. Serv. Co.,
285 F.3d 1046 (Fed. Cir. 2002) (en banc) (per curiam).....50, 53

Lucent Techs., Inc. v. Gateway, Inc.,
525 F.3d 1200 (Fed. Cir. 2008) 35-36

Norian Corp. v. Stryker Corp.,
432 F.3d 1356 (Fed. Cir. 2005) 34-35

Pfizer, Inc. v. Teva Pharms., USA, Inc.,
429 F.3d 1364 (Fed. Cir. 2005) 51, 59

Pfizer Inc. v. Teva Pharms. USA, Inc.,
882 F. Supp. 2d 643 (D. Del. 2012).....49

Pitney Bowes, Inc. v. Hewlett-Packard Co.,
182 F.3d 1298 (Fed. Cir. 1999) 8

PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.,
355 F.3d 1353 (Fed. Cir. 2004) 50-51, 53-56, 59, 62

Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.,
517 F.3d 1364 (Fed. Cir. 2008) 20, 26-31, 37-38, 49

Rowe v. Dror,
112 F.3d 473 (Fed. Cir. 1997) 67-68

SanDisk Corp. v. Kingston Tech. Co.,
695 F.3d 1348 (Fed. Cir. 2012) 21, 50-53, 56-57, 59, 62

Schwarz Pharma, Inc. v. Paddock Labs., Inc.,
504 F.3d 1371 (Fed. Cir. 2007) 36

Telemac Cellular Corp. v. Topp Telecom, Inc.,
247 F.3d 1316 (Fed. Cir. 2001) 52

Toro Co. v. White Consolidated Indus., Inc.,
383 F.3d 1326 (Fed. Cir. 2004) 53

Valmont Indus., Inc. v. Reinke Mfg. Co., Inc.,
983 F.2d 1039 (Fed. Cir. 1993) 22

Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,
520 U.S. 17 (1997) 22, 39-40, 63, 67

OTHER AUTHORITIES

21 U.S.C. § 355 12

37 C.F.R. § 1.75 67

TABLE OF REFERENCES

Citation	Reference
Akimoto	U.S. Patent No. 4,997,838
Arsenyan	Arsenyan et al., *Influence of Methylcobalamin on the Antineoplastic Activity of Methotrexate*, Pharm. Chem. J. 12(10):1299-1303 (1978)
John	John et al., *Activity of Multitargeted Antifolate (Pemetrexed Disodium, LY231514) In Patients with Advanced Colorectal Carcinoma*, Cancer, 88:1807-13 (2000)
Ohmori	U.S. Patent No. 5,431,925
Worzalla	Worzalla et al., *Role of Folic Acid in Modulating the Toxicity and Efficacy of Multitargeted Antifolate, LY231514*, Anticancer Research, 18:3235-40 (1998)

STATEMENT OF RELATED CASES

There has not been any prior appeal in or from this district court civil action. This Court previously upheld the validity of U.S. Patent No. 7,772,209 and affirmed judgments of infringement of that patent against other manufacturers in *Eli Lilly and Company v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357 (Fed. Cir. 2017) (Prost, C.J.).

Eli Lilly and Company v. Hospira, Inc., No. 18-2126, -2127 (Fed. Cir.), is designated as a companion case to this appeal. Dkt. 22.

Additionally, the following pending cases will directly affect or will be directly affected by the Court's decision in these appeals: *Neptune Generics, LLC v. Eli Lilly and Company*, Nos. 18-1257, -1258, -1288, -1290 (Fed. Cir.); *Eli Lilly and Company v. Nang Kuang Pharm. Co.*, No. 1:14-cv-1647-TWP-MPB (S.D. Ind.); *Eli Lilly and Company v. Actavis LLC*, No. 1:17-cv-982-TWP-MPB (S.D. Ind.); *Eli Lilly and Company v. Amneal Pharms. LLC*, No. 1:17-cv-986-TWP-MPB (S.D. Ind.); *Eli Lilly and Company v. Jiangsu Hansoh Pharm. Grp. Co.*, No. 1:17-cv-2864-TWP-MPB (S.D. Ind.); *Eli Lilly and Company v. Apotex, Inc.*, No. 1:17-cv-2865-TWP-MPB (S.D. Ind.); *Eli Lilly and Company v. Eagle Pharms., Inc.*, No. 17-cv-1293 (MSG) (D. Del.); *Eagle Pharms., Inc. v. Eli Lilly and Company*, No. 18-cv-1121 (MSG) (D. Del).

STATEMENT OF THE ISSUES

1. Whether the district court erred in concluding that prosecution history estoppel does not bar Lilly from pursuing infringement under the doctrine of equivalents.

2. Whether the district court erred in concluding that the disclosure-dedication rule does not bar Lilly from pursuing infringement under the doctrine of equivalents.

3. Whether the district court clearly erred in finding that the administration of DRL's product is equivalent to the administration of pemetrexed disodium in the claims of the '209 patent.

STATEMENT OF THE CASE

Plaintiff-Appellee Eli Lilly and Company (Lilly) manufactures and sells ALIMTA®, a drug that treats certain types of lung cancer and mesothelioma. The active moiety in ALIMTA® is the antifolate pemetrexed. Lilly is the assignee of U.S. Patent No. 7,772,209 (the '209 patent), which claims a method of administering pemetrexed chemotherapy by pretreating patients with folic acid and vitamin B_{12} and then administering pemetrexed disodium. This method reduces the incidence of severe toxicities that can be associated with pemetrexed without compromising the drug's anticancer efficacy.

Lilly distributes ALIMTA® as a solid powder formulation of pemetrexed disodium. In this form, each pemetrexed molecule is ionically bonded to two sodium ions. ALIMTA®, however, is never administered as a solid. Appx3974, Appx4387-4390, Appx7811. Instead, it is dissolved in solution so it can be injected intravenously into a patient. *Id.* When pemetrexed disodium dissolves, the pemetrexed and sodium separate, or "dissociate," from each other, meaning that what is administered is a solution containing pemetrexed and sodium ions. Appx4384-4388, Appx4514-4515.

Defendants-Appellants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively DRL) filed a new drug application (NDA) with

the Food and Drug Administration (FDA) seeking approval to sell their own pemetrexed product prior to the expiration of the '209 patent. DRL is not the first competitor to seek approval for a pemetrexed product. The U.S. District Court for the Southern District of Indiana found, and this Court affirmed, that competitors seeking to market pemetrexed disodium products identical to ALIMTA® infringed the '209 patent, and that the claims had not been proven invalid. *Eli Lilly and Company v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357 (Fed. Cir. 2017).

DRL's case is different from the *Teva* appeal because DRL is attempting to avoid infringement by using a different salt form of pemetrexed, pemetrexed ditromethamine. That is, DRL's proposed product contains the same active antifolate moiety as ALIMTA® (pemetrexed), but in solid form the pemetrexed is attached to a different counter-ion.[1] Notwithstanding this difference, DRL relies on Lilly's clinical data for ALIMTA® to show the efficacy and safety of DRL's product.

After DRL notified Lilly that it was seeking FDA approval for its pemetrexed product, Lilly filed the infringement action giving rise to this

[1] Hospira, Inc., the appellant in the companion appeal to this case, *see* Dkt. 22, similarly seeks to market a pemetrexed ditromethamine product.

appeal. DRL moved for summary judgment on various grounds. The district court denied DRL's motion, and the case proceeded to trial on the issue of doctrine-of-equivalents infringement. After a bench trial, the district court entered judgment for Lilly, concluding that Lilly was not barred from asserting the doctrine of equivalents and that DRL was liable for infringement under that doctrine. DRL now appeals.

I. BACKGROUND.

A. Antifolates and Pemetrexed.

Human cells, whether normal or cancerous, must make DNA to divide and replicate. Appx48, Appx4141-4142, Appx4386. DNA synthesis requires compounds called "folates." *See id.* "Antifolates" are a class of drugs that inhibit certain enzymes that use folates for DNA synthesis, thus interfering with DNA production. Appx48-49, Appx4141-4142, Appx4386, Appx4405-4410, Appx8369. This interference allows antifolates to be effective chemotherapy agents; rapidly dividing cancer cells need DNA to grow and replicate, and antifolates impede their ability to make DNA. *Id.* Unfortunately, this mechanism can also affect healthy cells, particularly those that divide rapidly. *Id.* When antifolates interfere with DNA production in healthy cells, it can lead to severe and even fatal toxicities for patients

receiving antifolate chemotherapy. *Id.* These toxicities complicated the development of antifolates. Appx48.

Pemetrexed is an antifolate. Appx4385, Appx4442, Appx4709-4710, Appx8404-8405. During pemetrexed's development, Lilly discovered that pemetrexed's toxicities can be significantly reduced by pretreating patients with folic acid and a methylmalonic acid lowering agent like vitamin B_{12}. Appx48; *Teva*, 845 F.3d at 1361-62. Each claim of the '209 patent recites administering both folic acid and vitamin B_{12} (or, in claim 1, on which asserted claims 9 and 10 depend, a "methylmalonic acid lowering agent"), then administering pemetrexed disodium. Appx52-53.[2]

B. The Person of Ordinary Skill.

Because the '209 patent seeks to mitigate toxicities associated with chemotherapy and recites methods of administering chemotherapy to cancer patients, the person of ordinary skill in the art (POSA) to whom the '209 patent is directed must include a medical oncologist. Appx15-16, Appx4378-7381, Appx8370-8371, Appx8478-8480; *see Eli Lilly and Company v. Teva Parenteral Meds., Inc.*, 2014 WL 1350129 at *5 (S.D. Ind. Mar. 31, 2014), *aff'd*,

[2] In this action, Lilly asserted claims 9, 10, 12-15, 18, 19, 21, and 22 of the '209 patent. Appx1, Appx3974.

845 F.3d 1357; *Eli Lilly and Company v. Teva Parenteral Meds., Inc.*, 2012 WL 2358102, at *4 (S.D. Ind. Jun. 20, 2012).

C. Lilly's Claim Amendment During Prosecution.

DRL's theory of prosecution history estoppel is based on an amendment that Lilly made in the course of prosecuting U.S. Patent Application No. 10/297,821, an application leading to the '209 patent. Appx46.

Lilly initially sought independent claims directed to administration of "an antifolate" following pretreatment with a methylmalonic acid lowering agent (and in some claims folic acid), along with certain dependent claims reciting administration of ALIMTA®. Appx7859-7861. The examiner rejected all of these claims. Appx7863-7873. This included prior art rejections and a rejection of the claims reciting "ALIMTA" as indefinite for improperly using a trademark in a claim. *Id.*

Although DRL identifies several of these rejections, it cites only one to justify its claim of prosecution history estoppel: the examiner's rejection of certain claims as anticipated by the Arsenyan reference. *Compare* Br. 12-14, *with* Br. 37-55; *see* Appx7868. This is also the sole rejection that DRL focused on before the district court. *See* Appx1637-1641, Appx1647-1655, Appx2538-

2547, Appx3988-3997.[3] Arsenyan discloses administration of a vitamin B_{12} derivative to a mouse prior to the administration of methotrexate, an antifolate. Appx7868, Appx7880, Appx8504-8507, Appx9759-9763. Methotrexate is a different active chemical moiety—or as the district court referred to it, "active antifolate," *e.g.*, Appx35—from pemetrexed. *See* Appx7880, Appx8504-8507. Arsenyan makes no reference to different salt forms of methotrexate, pemetrexed, or any antifolate. *Id.*

In response to the Arsenyan rejection, Lilly amended its claims to replace administration of "an antifolate" with administration of "pemetrexed disodium." Appx7874-7878, Appx8403-8405, Appx8504-8507. Lilly explained at the time that the purpose of its amendment was to avoid the Arsenyan reference and its use of methotrexate by specifying a particular (and different) active antifolate, pemetrexed: "In particular, Arsenyan et. al. does not disclose pemetrexed disodium and does not disclose the use of vitamin B_{12} or a

[3] On appeal, DRL also mentions two obviousness rejections: one over Ohmori and John, and the other over Arsenyan, Ohmori, and Worzalla. Br. 13-14. Because DRL develops no argument on the relevance of these rejections, Lilly will not address them here. Similarly, DRL identifies Lilly's amendment to the title of the invention, Br. 14, 53-54, but this amendment is not relevant. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1312 (Fed. Cir. 1999).

pharmaceutical derivative *to reduce the toxicity associated with* the administration of pemetrexed disodium." Appx7880 (emphasis added). The toxicities associated with the administration of pemetrexed disodium come from the pemetrexed itself, which is what interacts with the various folate-utilizing enzymes. Pemetrexed disodium as a bonded compound does not cause any toxicities. It is never given to a patient as a solid, and pemetrexed cannot bind to the relevant enzymes unless and until it has dissociated from the sodium. Thus, the toxicities associated with the administration of pemetrexed disodium are the toxicities caused by pemetrexed once dissociated in solution; they do not relate to the salt form prior to administration. Appx4391, Appx8403-8405, Appx8504-8507. Accordingly, the reason for the amendment was to distinguish pemetrexed from methotrexate (which was included in the former claim language), not to distinguish pemetrexed disodium from other forms of pemetrexed (which all use the same active antifolate). Appx8403-8405, Appx8504-8507.

The examiner withdrew the Arsenyan rejection in light of Lilly's amendment. Appx7885-7888. When Lilly filed U.S. Application No. 11/776,329, which ultimately issued as the '209 patent, Lilly carried through the change from "an antifolate" to "pemetrexed disodium" in a

preliminary amendment. Appx46, Appx52-53, Appx5466-5470. The reason for this preliminary amendment was the same as the original amendment—to overcome the Arsenyan rejection. Appx8506.

D. Lilly's ALIMTA®.

ALIMTA® is sold as a lyophilized (freeze-dried) powder of pemetrexed disodium. Appx7819. Because ALIMTA® must be administered intravenously, its labeling states that this powder must be reconstituted (dissolved) in solution and then further diluted before it can be administered to a patient. Appx7811; *see* Appx4384-4390. Upon reconstitution, the pemetrexed ions dissociate from the sodium ions to which they were bound. Appx4384-4388, Appx4514-4515. It is only after pemetrexed has dissociated that it can provide a chemotherapeutic effect. Appx4391. When this solution is subsequently administered, the patient does not (and cannot) receive any "pemetrexed disodium" as a solid compound. Appx4386-4390, Appx7811.

The ALIMTA® label instructs that a patient must receive the claimed regimen of folic acid and vitamin B_{12} pretreatment before receiving ALIMTA®. Appx7811.

The administration of ALIMTA® in accordance with its labeling meets each limitation of the asserted claims. Appx4393, Appx8369.

E. DRL's NDA Product.

The pemetrexed product that DRL seeks to market contains pemetrexed ditromethamine, a different salt form of pemetrexed. Appx7786-7787. The labeling for DRL's product is almost identical to the labeling for ALIMTA®. *Compare* Appx7770-7807, *with* Appx7808-7834. Both recite the same indications, and both require folic acid and vitamin B_{12} pretreatment as claimed in the '209 patent. *Id.*; *see* Appx4399-4402, Appx8375-8377.

Like ALIMTA®, DRL's product is to be sold as a lyophilized powder. Appx7787. It must be reconstituted and diluted such that it is fully dissolved in solution before it can be administered. Appx4388-4390, Appx7774. As with ALIMTA®, the pemetrexed in DRL's product dissociates from the tromethamine ions to which it was bound in solid form. Appx4384-4386, Appx4514-4524, Appx4684-4685. This solution of DRL's product contains the same amount of pemetrexed as a solution of ALIMTA®. Appx4392-4393, Appx4704-4705, Appx6696-6700, Appx7210, Appx8377-8378.

II. THE DISTRICT COURT PROCEEDINGS.

Lilly filed this Hatch-Waxman patent infringement action against DRL in February 2016 after DRL notified Lilly that it had submitted an NDA for a pemetrexed ditromethamine product, along with a Paragraph IV certification.

Appx583-592; *see* 21 U.S.C. § 355(b)(2)(A)(iv).

The district court denied DRL's motion for summary judgment in December 2017. Appx23-43. As relevant here, the district court held that neither prosecution history estoppel nor the disclosure-dedication rule bar Lilly from pursuing infringement under the doctrine of equivalents. Appx34-39. With respect to prosecution history estoppel, the district court found that Lilly amended its claims during prosecution from "an antifolate" to "pemetrexed disodium" in response to the Arsenyan rejection, and that this amendment was made to avoid methotrexate, an antifolate that is "distinguishable from pemetrexed." Appx34-37. The district court concluded that the POSA would therefore understand that the rationale for Lilly's amendment—limiting the active antifolate to pemetrexed—was tangential to the equivalent in question, a different salt form (ditromethamine) of the same active antifolate (pemetrexed). *Id.* The district court thus held that prosecution history estoppel did not prevent Lilly from pursuing doctrine-of-equivalents infringement. *Id.*

Turning to the disclosure-dedication rule, the district court found that there was no disclosure of pemetrexed ditromethamine as an alternative to pemetrexed disodium in the specification of the '209 patent. Appx37-39. As

the district court recognized, and DRL never contested, the patent does not "expressly disclose pemetrexed ditromethamine." Appx38. The court also refused to find a disclosure based on a single citation in the specification of the Akimoto patent. Appx38-39. The district court explained that Akimoto "does not satisfy the disclosure-dedication rule's requirements of a specific identification" because it contains "a large generic genus" of compounds and "no POSA would understand Akimoto to specifically disclose pemetrexed, tromethamine, or pemetrexed ditromethamine." *Id.*

The parties proceeded to trial on the issue of infringement under the doctrine of equivalents. Lilly offered testimony from two experts: Dr. Bruce Chabner, a medical oncologist at Harvard Medical School, and Dr. Rodolfo Pinal, a pharmaceutical chemist at Purdue University with experience in drug formulation, drug solubility, and the chemistry of pharmaceutical salts. Appx4370-4443, Appx4496-4543; Appx8362-8406, Appx8475-8508, Appx8527-8559, Appx8587-8604.

After considering the testimony, exhibits, and arguments of the parties, the district court issued its findings of fact and conclusions of law. Appx9-22. As relevant to this appeal, the district court found that the '209 patent is aimed at solving the problem of "toxicity in patients receiving chemotherapeutic

treatment with pemetrexed," and claims a method "that mitigates the toxicity associated with pemetrexed treatment, using the vitamin pretreatment regimen of vitamin B_{12} and folic acid." Appx10-11. The district court confirmed its determination at summary judgment that regardless of whether pemetrexed disodium or pemetrexed ditromethamine is administered, the patient will receive an "intravenous solution of pemetrexed" to treat their cancer. Appx11-12. And it agreed with Lilly that the POSA must include someone with the skills of a medical oncologist. Appx12, Appx15-16.

The district court also found that the evidence at trial had no impact on its determination at summary judgment that neither prosecution history estoppel, nor the disclosure-dedication rule, barred Lilly from pursuing infringement under the doctrine of equivalents. Appx12-14.

With respect to prosecution history estoppel, the district court reiterated that the reason for Lilly's narrowing amendment—to "overcome a rejection in view of Arsenyan, a prior art article about a different antifolate, methotrexate"—was not somehow "unexplained," as DRL had argued, and that this reason was tangential to DRL's pemetrexed ditromethamine equivalent. Appx12-13. The district court also noted that by "arguing that Lilly could have drafted a better claim," DRL was improperly "collaps[ing] the

foreseeability exception with the tangential exception" as defined by the Supreme Court in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002). Appx12.

As to disclosure-dedication, the district court again recognized that pemetrexed ditromethamine is not expressly mentioned in the '209 patent. Appx13. In concluding that Akimoto did not sufficiently disclose pemetrexed ditromethamine, the district court found that the '209 patent did not incorporate Akimoto by reference, and that Akimoto was, at most, a "generic reference" encompassing thousands of compounds, only one of which was pemetrexed. Moreover, the district court held that Akimoto does not sufficiently disclose pemetrexed ditromethamine as an alternative to pemetrexed disodium. Appx14. In reaching these conclusions, the district court credited the testimony of Lilly's expert, Dr. Pinal, who explained the broad scope of what Akimoto encompasses. *Id.*

Finally, as to infringement by equivalents, the district court held that the administration of DRL's product would infringe the only disputed limitation in the asserted claims: "administration of pemetrexed disodium." Appx15-19, Appx3975. It found an insubstantial difference between administration of pemetrexed disodium and administration of pemetrexed

ditromethamine in the context of the claims. Appx17-19. At the point when either pemetrexed disodium or pemetrexed ditromethamine is administered to a patient, it was undisputed that both are fully dissolved in solution; the district court thus reasoned that in this context, the "two products will be identical" because the pemetrexed in each is fully dissociated from its respective "therapeutically irrelevant counterion." Appx17-18. The district court acknowledged that pemetrexed ditromethamine and pemetrexed disodium had different chemical properties but, relying on the unrebutted testimony of Dr. Chabner, agreed with Lilly that such differences were "irrelevant in the context of the claimed method." Appx18-19. Notably, the district court found that the definition of the POSA was "critical (and dispositive)" to the resolution of the equivalents analysis. Appx16.

Having concluded that DRL was liable for indirect infringement under the doctrine of equivalents (a finding that DRL does not appeal), Appx21, the district court entered judgment in favor of Lilly and against DRL, Appx1, 7; *see* Appx4261-4273; Dkt. 2, 22. This appeal followed.

SUMMARY OF ARGUMENT

I. The district court correctly concluded that prosecution history estoppel does not bar Lilly from asserting infringement by equivalents.

Lilly amended the claims of what became the '209 patent during prosecution, narrowing "administration of an antifolate" to "administration of pemetrexed disodium." Prosecution history estoppel does not preclude the doctrine of equivalents where the rationale for the amendment, as understood by the POSA from the prosecution history, bears no more than a tangential relation to the equivalent in question. That is precisely the case here: Lilly's amendment was made in response to a rejection over a reference (Arsenyan) that disclosed a different active antifolate (methotrexate). The undisputed record establishes that the POSA would understand this as an attempt to distinguish pemetrexed from other active antifolates like methotrexate. The district court properly applied this understanding in finding that Lilly's amendment had nothing to do with the equivalent in question, *i.e.*, the use of a different salt form of pemetrexed.

DRL attempts to impose a burden on Lilly to show why it elected to narrow the claims to "pemetrexed disodium" specifically rather than broader, alternative formulations that DRL can envision. But that fundamentally misconstrues the tangentiality analysis. The focus is on the *rationale* for the amendment Lilly *actually made*, not whether that same rationale could have led to different amendments or why Lilly picked one over another. DRL also

invokes a supposed rule that the tangentiality exception can never apply where the reason for the amendment and the equivalent at issue both concern the same claim element. This Court has never announced any such legal rule; to the contrary, it has applied the tangentiality exception in cases where the alleged equivalent involves the same claim limitation. The Court should do so again in this case.

II. The district court also correctly concluded that the disclosure-dedication rule does not bar Lilly from asserting the doctrine of equivalents. The parties agree that "pemetrexed ditromethamine" appears nowhere in the '209 patent or in any of the patents mentioned therein. Faced with this fatal obstacle to establishing disclosure, DRL hunts through the references in the '209 patent's specification for a non-existent disclosure of pemetrexed ditromethamine. As the district court correctly found, the disclosures to which DRL points—a large genus of compounds that includes pemetrexed, coupled with extrinsic evidence that tromethamine was a known, FDA-approved salt—simply are not a "specific disclosure" of pemetrexed ditromethamine as an alternative to pemetrexed disodium. Indeed, those references do not disclose pemetrexed or tromethamine at all, much less pemetrexed ditromethamine as an unclaimed alternative to pemetrexed disodium. The district court rightly

rejected this legally insufficient disclosure-dedication argument.

III. Finally, the district court did not err in finding that administration of pemetrexed ditromethamine was equivalent to administration of pemetrexed disodium in the claimed method. The district court relied on undisputed expert testimony that administering pemetrexed ditromethamine to a patient in need of chemotherapy is insubstantially different from administering pemetrexed disodium—in both cases the patient receives a solution containing the identical pemetrexed ions and therapeutically irrelevant counter-ions. DRL does not challenge this factual finding on appeal. Instead, DRL argues that the district court somehow ignored that the claims recite "methods for administering" and erred by considering the context of the claims: treating a cancer patient. This semantic dispute incorrectly characterizes what the district court did, and is devoid of substance. The claims recite methods of administering an effective amount of chemotherapy to a patient in need of that treatment (i.e., cancer patients) by pretreating the patient with folic acid and vitamin B12 to address the toxicities associated with pemetrexed. DRL repeatedly ignores this critical context, which is that the "methods for administering" are *to a patient who needs the pemetrexed chemotherapy*. These claims are thus about the medical activity of treating

cancer patients, not an issue of salt-form chemistry as DRL argued in the district court. Indeed, as the district court correctly found, everything actually recited in the claims relates to the administration of pemetrexed to treat a patient, not to some process of dissolving solid pemetrexed salts. And even if the Court were to accept DRL's characterization of the claims, there is still no reversible error in the court's conclusion that use of DRL's products is equivalent to using pemetrexed disodium because there is no evidence in the record that the chemical differences DRL identifies have any effect on the administration of either product.

STANDARD OF REVIEW

Whether Lilly has rebutted the presumption of prosecution history estoppel is a question of law reviewed *de novo*. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 344 F.3d 1359, 1367-78 (Fed. Cir. 2003) (en banc); *Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1371 (Fed. Cir. 2008). This legal determination may require the resolution of underlying facts, and those findings are reviewed for clear error. *Festo*, 344 F.3d at 1368-70 & n.3; *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1324 (Fed. Cir. 2009); *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1311-12 (Fed. Cir. 2008).

The applicability of the disclosure-dedication rule is a question of law reviewed *de novo*. *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1364 (Fed. Cir. 2012).

Infringement under the doctrine of equivalents is a question of fact, reviewed for clear error following a bench trial. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1311 (Fed. Cir. 2015).

ARGUMENT

I. PROSECUTION HISTORY ESTOPPEL DOES NOT BAR LILLY FROM PURSUING THE DOCTRINE OF EQUIVALENTS.

The district court correctly concluded that prosecution history estoppel does not bar Lilly from asserting infringement under the doctrine of equivalents. Appx12-13, Appx34-37.

DRL's claim for estoppel rests on Lilly's amendment during prosecution to recite administration of "pemetrexed disodium" rather than of "an antifolate," in light of a rejection over the Arsenyan reference. Br. 33-55. There is no dispute that this amendment triggers an initial presumption of prosecution history estoppel. *See Festo*, 344 F.3d at 1366-67.

That presumption is rebutted, however, because this case falls squarely within one of the three *Festo* exceptions to prosecution history estoppel: the reason for Lilly's amendment is tangential to the equivalent at issue, *viz.*, the

administration of pemetrexed ditromethamine rather than pemetrexed disodium in the claimed method.

A. The Reason for Lilly's Amendment Was Tangential to DRL's Proposed Pemetrexed Ditromethamine Equivalent.

1. The Tangentiality Exception Focuses on the Reason for an Amendment.

The doctrine of equivalents protects patentees from infringers who make "unimportant and insubstantial changes . . . which, though adding nothing, would be enough to take the copied matter outside the claim." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607 (1950); *Valmont Indus., Inc. v. Reinke Mfg. Co., Inc.*, 983 F.2d 1039, 1043 (Fed. Cir. 1993). The doctrine has a long history and "remain[s] a firmly entrenched part of the settled rights protected by the patent." *Festo*, 535 U.S. at 731; *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24-37 (1997).

In *Festo*, the Supreme Court adopted a two-step framework for evaluating the applicability of prosecution history estoppel. 535 U.S. at 740-41. The first step is to identify whether a narrowing amendment was made for a substantial reason related to patentability. *Id.* If so, the amendment is presumed to disclaim "the territory between the original claim and the amended claim." *Id.* at 740. This presumption, however, is not just a

"complete bar by another name." *Id.* at 741. An amendment made during prosecution concedes "that the patent does not extend as far as the original claim," but "[i]t does not follow . . . that the amended claim becomes so perfect in its description that no one could devise an equivalent." *Id.* at 737-38. Instead, the second step of the framework asks whether one of the following three scenarios exists:

> [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; *Festo*, 344 F.3d at 1368-70. These scenarios are independent exceptions to the presumption of estoppel. *Id.*

With respect to the tangentiality exception—the exception the district court found here—the 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. This reason must be "objectively apparent" and "discernible from the prosecution history record[.]" *Id.* Because the tangentiality determination "necessarily requires focus on the context in which the amendment was made," it may require "testimony from those skilled

in the art as to the interpretation of that record." *Id.* at 1370. So long as the patentee's arguments are grounded in the prosecution record, any concerns about the public notice function of the claims are satisfied. *See id.*

2. The District Court Correctly Concluded That the Reason for Lilly's Amendment Is Tangential to DRL's Proposed Equivalent.

Because there is no dispute that the first step of the *Festo* analysis is satisfied, the prosecution history estoppel issue before the Court is whether, as the district court held, the tangentiality exception applies.

Notably, DRL does not challenge the central facts on which the district court's decision is based. The parties agree that the amendment giving rise to the presumption of estoppel narrowed administration of "an antifolate" to administration of "pemetrexed disodium," and they agree that this amendment was made in response to a rejection over Arsenyan, which teaches the administration of methotrexate in combination with a vitamin B_{12} derivative. Br. 33-38, 42-43; Appx7868, Appx7880, Appx8504-8507, Appx9759-9763.

After considering testimony as to how the POSA would understand the prosecution history, the district court found that methotrexate, as described in Arsenyan, is a different active antifolate from pemetrexed. Appx12-13,

Appx34-37, Appx8403-8405, Appx8504-8507. The district court further found that the reason for Lilly's amendment was to distinguish the universe of all antifolates—including Arsenyan's methotrexate—from just one active antifolate, pemetrexed, and that what distinguishes methotrexate and pemetrexed is entirely unrelated to the different salt forms of a single active antifolate—*e.g.*, pemetrexed ditromethamine and pemetrexed disodium. *Id.* DRL does not explain how the district court erred in making these findings.

Nor could DRL do so: the prosecution history fully supports these findings. Lilly explained to the examiner that Arsenyan does not disclose the use of vitamin B_{12} to "reduce the toxicity associated with the administration of pemetrexed disodium," and the examiner withdrew the Arsenyan rejection in response. Appx7880, Appx7888. While that statement mirrors the "disodium" claim language, it is undisputed that the "toxicity associated with the administration of pemetrexed disodium" is the toxicity of pemetrexed itself, rather than of any particular salt form. Appx8403-8405, Appx8505. Pemetrexed and sodium dissociate from each other in solution before being administered according to the claims. It is dissociated pemetrexed that binds to folate enzymes and causes toxicities, not sodium or pemetrexed disodium. *Id.* The claimed invention, and Lilly's response to the examiner, addresses

toxicities only from dissociated pemetrexed. Thus, the POSA would understand that the initial pemetrexed salt form is irrelevant to distinguishing Arsenyan, and the relevant point of distinction is the presence of pemetrexed (as opposed to methotrexate or some other active antifolate) in the solution that is administered. Appx8403-8405, Appx8504-8507. Additionally, nothing in the prosecution history discusses different salt forms of any antifolate, much less of pemetrexed specifically. *Id.*; *see* Appx7859-7897.

For these reasons, the district court correctly identified the reason for Lilly's amendment, and correctly concluded that the choice of salt form of that antifolate, and thus DRL's use of pemetrexed ditromethamine, is "peripheral, or not directly relevant" to—and in fact has nothing to do with—that reason. *Festo*, 344 F.3d at 1369; *see also Insituform Techs., Inc. v. CAT Contracting, Inc.*, 385 F.3d 1360, 1370 (Fed. Cir. 2004).

3. This Court's Precedents Support the District Court's Conclusion.

The district court correctly recognized that this Court's precedents support the application of the tangentiality exception here. The district court analogized to *Regents*, 517 F.3d at 1369, where this Court considered claims directed to improving the detection of chromosome abnormalities using DNA testing. *Id.* The claims at issue had been narrowed by the inclusion of a

"blocking nucleic acid" limitation. *Id.* at 1376. "Blocking" was one of several methods available to "disable the hybridization capacity of repetitive sequences" and make it easier to identify abnormalities. *Id.* at 1368-69. The patentee made this amendment to overcome an obviousness rejection in light of prior art that claimed another disabling method. *Id.* at 1378.

The accused equivalent in *Regents* also used a blocking method to disable hybridization, but differed with respect to the "nucleic acid" portion of the amendment. *Id.* at 1376. "Nucleic acid" was construed to require actual human DNA or RNA, meaning that the alleged equivalent—which used synthetic nucleic acids—was outside the literal scope of the claims. *Id.* The alleged infringer argued that the patentee was estopped from pursuing the doctrine of equivalents because the amendment had excluded methods of blocking that did not involve a "nucleic acid" as the term was construed. *Id.*

This Court rejected that argument, finding that the tangentiality exception applied. *Id.* at 1376-78. It recognized that the prosecution history made clear 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.* at 1378. The Court also noted that "nucleic acid" was not at issue in the rejection or amendment, and that "none of the cited references

concerned the type of nucleic acid that could perform the blocking, or mentioned the accused equivalent." *Id.*

As the district court recognized, Lilly's amendment ("pemetrexed disodium") is analogous to the amendment in *Regents* ("blocking nucleic acid"). Appx12-13, Appx34-37. Just as the reason for the "blocking nucleic acid" amendment in *Regents* was to limit the claim to the use of "blocking," and did not bear on the specific agent used for that blocking, the reason for the "pemetrexed disodium" amendment here was to narrow the claim to one active antifolate (pemetrexed) and does not bear on the specific salt form of that antifolate. In *Regents*, the use of a synthetic nucleic acid instead of a natural "nucleic acid" was appropriately deemed tangential to the reason for the amendment. Here, the use of a ditromethamine salt instead of a disodium salt is likewise tangential to the reason for the amendment.

DRL and its amicus attempt to distinguish *Regents* by arguing that "nucleic acid" was elsewhere in the claims prior to the amendment and never narrowed during prosecution, and that this fact motivated the Court's tangentiality finding. Br. 51-52; Actavis Br. 25-26. That misreads both *Regents* and the relevant claim. The "nucleic acid" previously recited in the independent claim at issue differs from the "blocking nucleic acid" added by

the narrowing amendment. Before the amendment, independent claim 28 recited "labeled nucleic acid fragments" corresponding to the DNA to be detected. *Regents*, 517 F.3d at 1377. That limitation remains in the issued claim as "labeled nucleic acid." *Id.* at 1369. The "blocking nucleic acid," by contrast, disables the hybridization capacity of repetitive segments in the labeled nucleic acid. *Id.* at 1369.[4] Amending the claims to require a "blocking nucleic acid" introduced a new limitation.

DRL makes a further attempt to distinguish *Regents* by arguing that the amendment at issue involved two aspects of a claim limitation ("blocking" and "nucleic acid"), while Lilly's amendment from "antifolate" to "pemetrexed disodium" supposedly involved only a single "aspect" of the limitation. Br. 51-52. That is incorrect. "Blocking nucleic acid" refers to a single substance and was added to the claim at one time as a single limitation. This Court never suggested that the reason why the tangentiality exception applied was that the limitation added during prosecution had two different "aspects,"

[4] Even before the amendment, dependent claim 99 made the distinction among the different nucleic acids clear: it recited the use of "unlabeled repetitive nucleic acid fragments" to "block[] the labeled repetitive nucleic acid fragments." *Regents*, 517 F.3d at 1377.

nor did it articulate a test for determining when a claim limitation can be divided into "aspects."

To the extent there are two "aspects" to the blocking nucleic acid, there are likewise two aspects to pemetrexed disodium: an active antifolate (pemetrexed) and a specific salt form (disodium). *See* Appx12-13, Appx34-37. In both *Regents* and here, the reason for the amendment dealt with the first aspect: "blocking" as opposed to other means of disabling hybridization in *Regents*, and pemetrexed as opposed to another active antifolate (methotrexate) here. In both cases the second aspect, which here is the particular salt form of pemetrexed, was immaterial. DRL's attempt to analyze the claim limitation in *Regents* as having two aspects, only one of which bore on the reason for the amendment, only highlights the similarity of *Regents* to the present case, including the reasons for applying the tangentiality exception here.

The conclusion that Lilly's amendment was tangential is further demonstrated by *Insituform*. The patent in *Insituform* concerned a method for repairing pipes by installing resin-impregnated liners. 385 F.3d at 1362-63. During prosecution, the patentee narrowed its claims, which initially required multiple vacuum sources to inject resin, to require only a single

vacuum placed near where the resin was injected. This amendment was made to distinguish prior art that disclosed a single vacuum far away from the resin source. *Id.* at 1369. The proposed equivalent sought to use multiple vacuum sources, and thus fell within the scope of what was excluded by the amendment. *Id.* at 1369-70. This Court held that prosecution history estoppel did not apply because the reason for the amendment was to distinguish prior art based on the location of the vacuums, rather than the number of vacuum sources. *Id.* The Court did so even though the patentee had, by narrowing his claims, excluded products that were unrelated to the prior art at issue and did not need to be excluded in order to avoid it. *Id.*

Both *Regents* and *Insituform* are therefore on all fours with this case. As in those cases, DRL's proposed equivalent involves an aspect of the invention (the salt form) that has nothing to do with the asserted prior art (Arsenyan) or the objectively apparent reason for Lilly's amendment (the identity of the active antifolate). Accordingly, the narrowing amendment (from antifolates as a class to pemetrexed disodium) was only tangential to the accused equivalent—pemetrexed ditromethamine.

B. DRL Misstates the Test for Tangentiality.

DRL's principal argument on appeal is that the district court

"misapprehended and misapplied" the tangentiality exception. Br. 37-55. But it is DRL that does so, by mischaracterizing what the district court held and improperly attempting to inject new constraints into the tangentiality analysis that have no basis in precedent.

1. DRL Misconstrues the District Court's Analysis.

DRL first constructs a straw-man version of the district court's decision, and then proceeds to try to knock it down. DRL argues that the district court found the tangentiality exception to apply on the basis that "Lilly surrendered more than it needed to distinguish the cited Arsenyan prior art," *i.e.*, that it was unnecessary for Lilly to have narrowed the claims to "pemetrexed disodium" rather than some broader language that would have encompassed DRL's product. Br. 37. The district court held nothing of the sort. Instead, it was properly focused on comparing the *reason* for Lilly's amendment to DRL's proposed equivalent—exactly what the law requires.

The district court began its tangentiality analysis by determining that the reason for Lilly's narrowing amendment was "to overcome a rejection in view of Arsenyan, a prior art article about a different antifolate, methotrexate." Appx12; *see supra* at 12, 14-15. The district court concluded that the POSA would thus understand that the purpose of the narrowing

amendment was to claim a particular active antifolate, pemetrexed. It also observed that the "POSA would understand that pemetrexed is the active antifolate" in both pemetrexed disodium and pemetrexed ditromethamine. Appx35. Accordingly, it concluded that the rationale for the amendment was tangential to the choice of salt form of pemetrexed in DRL's proposed equivalent. Appx13, Appx37. The district court's analysis, in other words, correctly compared the reason for the amendment to the equivalent in question.

Before the district court, DRL made the same argument it repeats now that 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." Appx12 (quoting Appx3990); Br. 43-47. The district court correctly recognized that Lilly was not making this argument, but rather had adequately explained the reason for the amendment and how it was tangential to the equivalent in question. Appx12-13, Appx34-37. Thus, not only did the district court not commit the error that DRL asserts, but it explicitly made clear that it was not doing so.

2. DRL's Focus on What the Patentee "Surrendered" Misconstrues the Tangentiality Analysis.

a. DRL argues that the tangentiality exception is unavailable to Lilly because the "consequences of narrowing amendments in prosecution" are determined by the scope of what was "actually surrendered." Br. 38-47. DRL appears to be arguing that the tangentiality exception cannot apply when an accused product was within the pre-amendment scope of a claim, but is outside the amended scope.

That is not the law. The tangentiality exception is not focused on the *fact* that claim scope was surrendered, but rather on *why* a particular amendment was made. Indeed, the Supreme Court has made clear that the *Festo* exceptions identify amendments that "cannot reasonably be viewed as surrendering a particular equivalent." *Festo*, 535 U.S. at 740-41. That statement assumes that the exceptions apply even though the claims were narrowed so as to "surrender" the relevant scope—contrary to DRL's putative rule that tangentiality cannot be found when the equivalent falls within the scope of the narrowing. Tellingly, none of the cases that DRL relies upon announces any such rule, and this Court's precedents are inconsistent with it.

In *Norian*, for example, the patentee argued that the prosecution history did not trigger *Festo* at all. *Norian Corp. v. Stryker Corp.*, 432 F.3d

1356, 1362-63 (Fed. Cir. 2005). The Court rejected that argument because it determined that the proposed equivalent fell within the territory presumptively surrendered by the narrowing amendment. *Id.* at 1363. The only reason the Court stopped its analysis there was because the patentee "d[id] not suggest that th[e] case falls within one of the exceptions . . . set forth by the Supreme Court in *Festo*." *Id.* Here, of course, Lilly does argue, and the district court held, that this case falls within the tangentiality exception. *Norian*, which did not consider tangentiality or any other exception, is completely inapposite.

In *Lucent*, the Court first determined that the presumption of prosecution history applied because the proposed equivalent fell within the "territory between the original claims and the amended claims," but then separately considered whether the tangentiality exception applied. *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1218 (Fed. Cir. 2008). Although the *Lucent* Court ultimately rejected the tangentiality exception, it did not—contrary to DRL's arguments—do so because the accused equivalent was within the territory surrendered by the narrowing. Rather, having determined that the accused equivalent was within the territory surrendered by the narrowing, the Court went on to compare the reason for the amendment

and the accused equivalent, and concluded on the facts of the case that there was "clearly more than a tangential relationship" between them. *Id.*

The other cases DRL cites similarly fail to help its argument. In *Schwarz*, for example, the patentee narrowed a claim to the use of one particular stabilizer, thereby excluding an equivalent "MgO" stabilizer. *Schwarz Pharma, Inc. v. Paddock Labs., Inc.*, 504 F.3d 1371, 1375-78 (Fed. Cir. 2007). Unlike Lilly, Schwarz did not argue that the alleged equivalent was unrelated to the reason for its amendment to overcome the prior art rejection. *Id.* Instead, it sought to invoke the tangentiality exception by arguing that in hindsight, it could have overcome a rejection without narrowing its claim. *Id.* at 1377-78. Here, Lilly has never argued, and the district court did not determine, that the tangentiality exception applies because Lilly could have overcome Arsenyan without amending its claims to exclude pemetrexed ditromethamine, if only it had made different decisions during prosecution. Rather, the court looked to the amendment Lilly *actually made* and the objectively apparent reason for that actual amendment as compared to the accused equivalent.

Likewise, *Integrated Technology* involved a "digital viewing system" where a "viewing window" inspected certain probes used in producing

semiconductor wafers. *Integrated Tech. Corp. v. Rudolph Techs., Inc.*, 734 F.3d 1352, 1355 (Fed. Cir. 2013). The equivalent involved a system in which the probes did not make contact with the viewing window. *Id.* Integrated Technologies could not establish tangentiality because it had explicitly relied on contact between the probe and the window to distinguish the prior art. *Id.* at 1358-59. Again, the Court's focus was on the *reason* for the amendment, not the scope of what was surrendered. Here, in contrast to *Integrated Technologies*, the distinguishing feature of DRL's equivalent—the salt form of pemetrexed—was irrelevant to the reason for Lilly's amendment. [5]

Not only is DRL's rule unsupported by these cases, but it is flatly inconsistent with *Regents* and *Insituform*. In those cases, as discussed above, the proposed equivalent was within the territory surrendered by the narrowing amendment, but the tangentiality exception nevertheless was found to apply. *Regents*, 517 F.3d at 1377-78; *Insituform*, 385 F.3d at 1369-70.

In *Regents*, the synthetic nucleic acids in the equivalent were within the

[5] DRL also cites *International Rectifier Corp. v. IXYS Corp.*, 515 F.3d 1353 (Fed. Cir. 2008), Br. 40-41, but that case also involved a fact-bound determination based on the reasons for the amendment rather than the scope of what was surrendered; the reason for the amendment was to limit the claims to "adjoining" structures, and that was not merely tangentially related to an equivalent that did not involve "adjoining" structures. *Id.* at 1359.

territory "surrendered" by the narrowing amendment. 517 F.3d at 1377-78. By DRL's logic, that should have ended the analysis, and the tangentiality exception should not have applied, because the patentee "actually surrendered" the proposed equivalent. *See* Br. 39. But this Court held exactly the opposite, finding tangentiality because the reason for the amendment was tangential to the type of nucleic acid. *Regents*, 517 F.3d at 1377-78.

Similarly, in *Insituform*, the proposed equivalent, using multiple "vacuum sources," fell within the scope of the original claims and was excluded by narrowing the claims to a single vacuum source. 385 F.3d at 1368-70. But once again, that putative "surrender" did not end the analysis. Rather, because the reason for the amendment pertained to the location rather than the number of vacuum sources, this Court found that the tangentiality exception applied. *Id.*

DRL is simply incorrect to argue that pemetrexed ditromethamine is not tangential to the reason for the amendment because it is "directly within the path of" Lilly's narrowing from "antifolates" to "pemetrexed disodium." Br. 43-44. That is not the test. If it were, *Regents* and *Insituform* would have come out the other way, and the exception would be eviscerated. The test, rather, is whether the asserted equivalent is tangential to the *reason* Lilly

made that narrowing. The district court correctly applied that test and found that it was.

b. Amicus curiae Actavis LLC (Actavis) echoes DRL's misguided argument that the district court's tangentiality finding was based on a notion that "Lilly may have surrendered more than necessary to secure approval for its patent." Actavis Br. 5. The additional cases Actavis cites do nothing to help DRL's case. *Id.* at 14-20.

First, Actavis cites the Supreme Court's decision in *Warner-Jenkinson* for the proposition that "a patentee's surrender is not limited to what was needed to overcome a patentability rejection." *Id.* at 16-18. But *Warner-Jenkinson* was not a case about tangentiality or indeed any of the exceptions to prosecution history estoppel. *See* 520 U.S. at 30-34. It addressed whether the doctrine of prosecution history estoppel existed in the modern era at all, and if so, whether it applied in cases where a patentee's amendment narrowed the claim more than necessary to overcome a rejection. *Id.* at 32-33. The Court answered both questions in the affirmative. But it did *not* hold that the tangentiality exception to prosecution history estoppel could not be established in such circumstances; it did not consider the tangentiality exception, nor could it have, as it predated *Festo*; and it expressly remanded

the case to develop a record on the reasons for the amendment in question. *Id.* at 33-34. Nothing in *Warner-Jenkinson* is inconsistent with the district court's holding here, which was based on uncontroverted evidence about the reason for Lilly's amendment.

Actavis next cites *Biagro Western Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296 (Fed. Cir. 2005). Actavis Br. 18. The amended claim in *Biagro* involved a concentration limitation, in which a "phosphorous-containing acid or salt" was "about 30 to about 40 weight percent" of a fertilizer compound. *Id.* at 1299. This amendment was made to overcome prior art with a different concentration. *Id.* at 1306. Rejecting an argument that the patentee could have claimed a broader range, this Court held that because the reason for the amendment was to focus on a particular concentration range, and the accused equivalent involved a concentration outside that range, the reason for the amendment was not tangential to the accused equivalent. *Id.* Nothing in *Biagro* purports to establish a categorical limitation on the tangentiality exception as Actavis claims, nor that the analysis turns on whether the patentee's narrowing "surrendered" the equivalent. Instead, the *Biagro* Court simply performed the same tangentiality analysis as the district court did here, and came to the fact-bound conclusion that the tangentiality

exception did not apply in that case.

Finally, Actavis turns to *Felix v. American Honda Motor Company*, 562 F.3d 1167 (Fed. Cir. 2009). Actavis Br. 18-19. *Felix*, like the other cases, simply found a lack of tangentiality on different facts, and does not suggest that the district court erred. The patent at issue in *Felix* claimed a "built-in storage compartment" in the bed of a pickup truck. *Id.* at 1171. Felix's initial claim was rejected in light of prior art which disclosed particular structural features of such a compartment: "a channel, a[n] inner lip and a weathertight gasket mounted on the inner lip." *Id.* at 1174 (alteration in original). In response, Felix narrowed the independent claim by adding two separate limitations: "a channel" including a flange, and a "weathertight gasket mounted on said flange." *Id.* at 1174-75. The alleged equivalent included a gasket affixed to the lid of the structure rather than to the flange. *Id.* at 1176.

Felix argued that the tangentiality exception applied because his narrowing amendment was made to overcome prior art involving a channel. *Id.* at 1184. This Court refused to apply the tangentiality exception, not because it analyzed tangentiality in a manner inconsistent with what the district court did here, but for two reasons particular to the facts of the case. First, the prosecution record discussed not only the channel, but also an "other

structure" that, the Court reasoned, could have included the gasket. *Id.* That belied Felix's argument, and also meant that it was not "objectively apparent" that the reason for the amendment was unrelated to the equivalent at issue. *Id.* That is nothing like the case here, where the only issue in prosecution was the choice of active antifolate, there is no reference to the salt form having any significance, and the unrebutted testimony before the district court was that the POSA would recognize that the form of pemetrexed was completely irrelevant to any issue of patentability. *See* Appx8403-8405, Appx8504-8507.

Second, the Court noted that Felix's asserted rationale for the amendment was undermined by his inclusion in prosecution of two separate structural components, the channel and the gasket, both of which were in the prior art. 562 F.3d at 1174, 1184. Here, by contrast, Lilly made one amendment, narrowing one generic limitation ("antifolate") to "pemetrexed disodium." The "disodium" part is not a separate, newly added structural component analogous to the separate "gasket" in *Felix*. Pemetrexed disodium was simply the specific salt form of the antifolate used in clinical trials, and already present (under the trade name "ALIMTA") in the dependent claims. Appx49, Appx50-52, Appx7861. The fact that the amended claim recited pemetrexed disodium specifically does nothing to undermine the district

court's finding that the purpose of the amendment was to narrow the genus of antifolates in response to the Arsenyan rejection and, particularly, its disclosure of the antifolate methotrexate.

Felix therefore did not announce a new test for the tangentiality exception under which Felix lost because of what he had "surrendered"; it simply applied the same standard that the district court applied in this case to a significantly different set of facts.

3. The Tangentiality Analysis Depends on the Reason for the Actual Amendment Lilly Made, Not the Reason It Did Not Make an Alternative, Broader Amendment.

DRL also asserts that Lilly cannot show that the tangentiality exception applies because it has not explained why it chose to claim "pemetrexed disodium" instead of broader language that would have encompassed DRL's product (such as, according to DRL, "pemetrexed"). Br. 42-47; *see* Actavis Br. 14-20. DRL is incorrect.

a. Under established precedent, the question for tangentiality is the reason that Lilly made the amendment it *actually made*. Nowhere does *Festo* or its progeny demand an explanation for why a patentee chose to use the particular amendment it did instead of other hypothetical amendments that it might have considered or that an accused infringer can concoct that would also

have been consistent with the reason for the amendment. And tellingly, both DRL and Actavis fail to cite a single case in which any court has undertaken such an analysis. The question the cases ask is far simpler: whether the reason the patentee narrowed the claim is no more than tangentially related to the equivalent. The district court correctly performed that analysis and concluded that the amendment here was tangential to DRL's equivalent.

A requirement for courts to consider hypothetical alternative amendments would undermine the principle that tangentiality must be evaluated based on what is apparent from the prosecution history, *Festo*, 344 F.3d at 1369-70, and would eviscerate the tangentiality exception. When the tangentiality exception applies, as it does here, the prosecution record reveals the reason for the amendment. The logic of the tangentiality exception and its focus on the prosecution record falls apart, however, if the patentee must also establish why it chose a particular amendment as compared to others that a challenger in litigation can come up with. The prosecution history, while revealing the rationale for the amendment that was made, will frequently *not* reveal why the patentee chose to insert Option A instead of Option B when both are consistent with the rationale for the amendment. And there is no reason to expect the prosecution history to address the reasons for using

certain language that excluded the equivalent instead of alternative, broader language encompassing the equivalent when the amendment was focused entirely on something else. Thus, here, the fact that the prosecution record says nothing about different salt forms of pemetrexed is evidence of tangentiality, not a problematic failure to explain the reason for Lilly's amendment. *See Insituform*, 385 F.3d at 1370.

b. Additionally, as the district court aptly recognized, DRL's approach improperly collapses the tangentiality exception with the separate exception set forth in *Festo* that asks whether the equivalent would have been foreseeable at the time of the amendment. *See* Appx12, Appx35; *see also Festo*, 344 F.3d at 1369-70. Whether, as DRL puts it, "Lilly knew how to discuss 'different salt forms of pemetrexed' when it wanted to," Br. 44, has nothing to do with whether the amendment that Lilly actually made bore more than a tangential relationship to other forms of pemetrexed. Rather, it is a question of whether Lilly could have foreseen and claimed other forms of pemetrexed, which is not part of the tangentiality analysis.

For its part, Actavis goes a step further and argues that there are no separate *Festo* exceptions at all; *Festo*, it claims, "did not announce three completely separate exceptions to estoppel," but rather should be limited to

cases in which the patentee "could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." Actavis Br. 29 (quoting *Festo*, 535 U.S. at 741).

That is flatly contrary to the Supreme Court's announcement of three separate exceptions, and wholly ignores this Court's binding precedents interpreting the Supreme Court's decision in *Festo*. On remand in *Festo*, this Court reiterated *en banc* that tangentiality is a *way* in which a patentee can show that it "could not reasonably be expected" to have drafted a claim encompassing the equivalent. 344 F.3d at 1365. Put another way, the three *Festo* exceptions are examples of situations in which the language upon which Actavis now seizes is satisfied.

If a patentee was making an amendment for one reason, and in so doing excludes an equivalent that is unrelated to the reason for the amendment, the tangentiality exception excuses the patentee's failure to claim that equivalent. Foreseeability, in contrast, addresses a different situation, not relevant here, where the equivalent may squarely relate to the reasons why the claim was narrowed, but the patentee could not have known at the time what its amendment was giving up, for example because of later technological developments. *Id.* at 1369. There is no basis to engraft a foreseeability

requirement into the tangentiality analysis or to treat foreseeability as somehow relevant here. Lilly has not asserted the foreseeability exception, it was not the basis of the district court's ruling, and the district court expressly considered and rejected DRL's invitation to conflate the two analyses. Appx12, Appx35. The district court's analysis of tangentiality—and its decision *not* to consider foreseeability—was correct.

4. The Tangentiality Exception Is Not Precluded Because Lilly's Rationale and DRL's Proposed Equivalent Involve the Same Claim Limitation.

DRL also argues for the legal rule that the tangentiality exception is unavailable whenever "the reason for the amendment and the equivalent in question both relate to the same claim element"—here, the "administration of an antifolate" limitation in the original claims. Br. 47-49. DRL calls this principle a "clear guidepost" established by this Court's decisions in *Honeywell* and *Biagro*. Br. 47-48. That is incorrect; this Court has never announced such a rule, and its tangentiality cases are inconsistent with this rule. *Honeywell* and *Biagro* are simply fact-bound applications of the normal tangentiality standard to specific scenarios.

Honeywell, for example, involved a patented system that controlled surges in airflow to an auxiliary power unit used in airplanes. 523 F.3d at 1306.

The patentee had initially pursued broad claims that encompassed multiple mechanisms for managing airflow, but those claims were rejected over prior art that disclosed a mechanism with "P and Delta P sensors." *Id.* at 1311. The patentee represented in litigation that its claims were narrowed in response to this rejection. *Id.* The proposed equivalent, like the prior art, used P and Delta P values to manage airflow. *Id.* The district court refused to apply the tangentiality exception, finding that "both the prior art and the equivalent in question involved the same flow-related measurement and the use of that measurement is directly related to the rationale underlying the amendments," and this Court affirmed. *Id.* at 1311, 1316. *Honeywell* did not purport to establish a broad bar to the tangentiality exception whenever the reason for the amendment and the equivalent concern the same limitation.

Biagro also says nothing in support of the rule that DRL proposes. There, this Court recognized that the reason for the amendment was to select a particular concentration of fertilizer, and thus held that the reason for the amendment was not tangential to the accused equivalent, which used a concentration outside the claimed range. 423 F.3d at 1306. *Biagro* did not hold, or even suggest, that the tangentiality exception is precluded in every case where the reason for the amendment and the accused equivalent touch on

the same claim limitation.

Not only do DRL's cases fail to support its proposed rule, but its rule is directly contradicted by *Regents*, where the independent claim was narrowed to require a "blocking nucleic acid" limitation. 517 F.3d at 1377. The accused equivalent related to exactly this limitation: it performed "blocking" but not with a "nucleic acid" as construed by the Court. And yet, despite this, the Court applied the tangentiality exception. *Id.* at 1378. DRL's notion that tangentiality can never apply when the reason for the amendment and the alleged equivalent involve the same claim limitation is impossible to square with *Regents*.[6] It runs directly contrary to this Court's long-held recognition that the tangentiality exception turns on the particular facts and circumstances of a case, and that there is "no hard-and-fast test for what is and what is not a tangential relation." *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1291 (Fed. Cir. 2010); *see Festo*, 344 F.3d at 1369. And as the district

[6] DRL does not identify any decision from any court that adopts the rigid approach to tangentiality it advocates. To the contrary, that approach was rejected by the district court that has considered the issue. *See Pfizer Inc. v. Teva Pharms. USA, Inc.*, 882 F. Supp. 2d 643, 728-29 & n.79 (D. Del. 2012). It also is inconsistent with *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 457 F.3d 1293, 1308-09, 1314-15 (Fed. Cir. 2006), where a single limitation was at issue but this Court nevertheless conducted a searching inquiry into what the prosecution record revealed about the reason for the amendment.

court correctly found, the facts here compel a conclusion that the reason for the amendment was tangential to the accused equivalent. The district court's decision regarding prosecution history estoppel should be affirmed.

II. THE DISCLOSURE-DEDICATION RULE DOES NOT BAR LILLY FROM PURSUING THE DOCTRINE OF EQUIVALENTS.

Independent of its arguments about prosecution history estoppel, DRL asserts that the disclosure-dedication rule bars Lilly from pursuing the doctrine of equivalents. Br. 55-74. This rule bars recourse to the doctrine of equivalents when a patent discloses a specific alternative to a claim limitation in the specification, but does not claim that alternative. *Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054-55 (Fed. Cir. 2002) (en banc) (per curiam). In such circumstances, the patentee is deemed to have dedicated the specifically disclosed but unclaimed alternative to the public, and is not allowed to use the doctrine of equivalents to recapture the alternative. *Id.*

To dedicate an invention to the public, a 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" by reading the specification. *PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1360 (Fed. Cir. 2004). The patent must also identify the disclosed but not claimed material as "an alternative to a claim limitation." *SanDisk*, 695 F.3d at 1363-64 (quoting

Pfizer, Inc. v. Teva Pharms., USA, Inc., 429 F.3d 1364, 1379 (Fed. Cir. 2005)). A "generic reference in a written specification" does not, without more, "dedicate[] all members of that particular genus to the public." *Id.* at 1363 (quoting *PSC*, 355 F.3d at 1360).

Here, the district court held a trial on, *inter alia*, whether pemetrexed ditromethamine was disclosed but not claimed in the '209 patent. Properly applying the well-established standard, the district court found that the '209 patent does not disclose pemetrexed ditromethamine. DRL's assertions that the district court erred are entirely without merit.

A. The Specification of the '209 Patent Does Not Expressly Disclose Pemetrexed Ditromethamine.

The district court correctly recognized that the specification of the '209 patent does not expressly disclose "pemetrexed ditromethamine." Appx13-14, Appx38-39. There is no dispute that "pemetrexed ditromethamine" does not appear anywhere on the face of the patent. *See* Appx5445-5452, Appx4436-4437, Appx4532. Even DRL's own expert agreed that there is no description, discussion, or mention of either "pemetrexed ditromethamine" or "tromethamine" in the '209 patent. Appx4710.

That fact alone should end the analysis; there is no plausible argument that Lilly dedicated pemetrexed ditromethamine to the public without even

mentioning it. Only in very specific, narrow circumstances has this Court ever even acknowledged a possibility that the disclosure-dedication rule can apply without a disclosure in the specification of the patent-in-suit itself, and those circumstances involve disclosures that are tantamount to being in the specification: when a disclosure was made in a priority application, *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1297 (Fed. Cir. 2009), or when a disclosure was made in prior art expressly incorporated into the patent by reference, *SanDisk*, 695 F.3d at 1366. As the *SanDisk* Court explained, the subject matter of such documents "becomes effectively part of the host document as if it were explicitly contained therein." *Id.* (quoting *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001)).

In contrast, DRL's argument is premised on the notion that the doctrine applies because Lilly *cited* other patents that allegedly disclose pemetrexed ditromethamine. Br. 58-59; *see* Appx14, Appx38, Appx4438-4442. Specifically, DRL points to the following specification text:

> Preferred examples of antifolates include . . . pyrido[2,3-d]pyrimidine derivatives described by Taylor et al in U.S. Pat. Nos. 4,684,653, 4,833,145, [] 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 . . . .

Br. 10-11, 59 (citing Appx49). Nothing in this language adopts everything said in these references as part of the '209 patent; rather, it merely notes that they contain, somewhere within, "[p]referred examples of antifolates" that may be used with the claimed invention. Appx5448, Appx4437-4438, Appx4532, Appx4712. That is a far cry from the required disclosure in the '209 patent or a document that is "effectively part of" it. *SanDisk*, 695 F.3d at 1366.

DRL asserts that disclosure-dedication applies even in the circumstance presented here, where a disclosure appears in another document that has not been incorporated into the patent. Br. 57-58. But DRL misreads the principal case it cites in proposing to expand the disclosure standard: *Toro Co. v. White Consolidated Industries, Inc.*, 383 F.3d 1326 (Fed. Cir. 2004). *Toro* held only that a disclosure need not appear in the "Detailed Description of the Invention," but could also be found in other parts of the specification. *Id.* at 1334. That does not mean, as DRL suggests, that a disclosure can be found outside the specification altogether, such as in prior art that is not incorporated into the patent-in-suit. Rather, with the narrow, limited exceptions noted above, this Court's disclosure-dedication precedent uniformly requires an express disclosure in the specification. *See, e.g.*, *Johnson*, 285 F.3d at 1054-55; *Toro*, 383 F.3d at 1330, 1334; *PSC*, 355 F.3d at

1360. Because there undisputedly is no such express disclosure of pemetrexed ditromethamine in the specification here, DRL's disclosure-dedication argument must fail.

B. The Specification's Unincorporated Prior Art References Do Not Disclose Pemetrexed Ditromethamine.

In any event, the district court did not simply end its analysis with the observation that the '209 patent fails to disclose pemetrexed ditromethamine. Instead, it conducted the analysis that DRL urges, searching for relevant disclosures in the references that are merely cited in the '209 patent. But after that search, the district court correctly found that there was no disclosure of pemetrexed ditromethamine.

There is no dispute that none of the references cited in the specification expressly discloses pemetrexed ditromethamine. Moreover, it is undisputed that five of the references—the Taylor patents and the EPO application—do not even encompass pemetrexed. Appx4440-4442, Appx4720, Appx4726. The focus of DRL's arguments and evidence at trial and again on appeal, is the Akimoto patent. Br. 66-70; *see, e.g.*, Appx4001-4005, 4198-4203.

As the district court correctly recognized, "Akimoto and what was contained therein amounts to a generic reference which does not dedicate all members of a particular genus to the public." Appx14, Appx38-39. In reaching

this conclusion, the district court credited Lilly's expert, Dr. Pinal, who explained that Akimoto claims a structure—known as "Formula I"—that encompasses thousands of antifolate compounds, only one of which is pemetrexed. Appx14, Appx4532-4542; *see* Appx4438-4440, Appx7933. Identifying pemetrexed from the genus of Formula I compounds requires selecting the correct values for seven unique variables in the Formula I structure. Appx4533-4539, Appx7933. And of the nearly fifty specific compounds identified by Akimoto as examples of what is encompassed by Formula I, not one of them is pemetrexed, nor is pemetrexed expressly disclosed anywhere in Akimoto. Appx4338, Appx4548-4532, Appx4714-4715, Appx7939-7940. The district court was thus correct to recognize Akimoto as a "generic reference," Appx14, Appx38-39, one that does not "dedicate[] all members of that particular genus to the public," *PSC*, 355 F.3d at 1360.

On appeal, DRL does not attempt to explain how Akimoto sufficiently discloses pemetrexed. Instead, DRL claims that Dr. Pinal conceded that pemetrexed is disclosed in the Akimoto reference. Br. 59, 67. That is incorrect; as the district court recognized, Dr. Pinal made no such concession. Appx14. Rather, what Dr. Pinal actually testified is that Akimoto describes a genus containing thousands of antifolates and that pemetrexed is one (among

thousands) of the antifolates *included* in that genus—but, contrary to DRL's assertions, he explained that it is *not* specifically disclosed. Appx4533-4542, Appx4561. It is well-settled that a "generic reference in a written specification" does not, without more, "dedicate[] all members of that particular genus to the public." *SanDisk*, 695 F.3d at 1363-64 (quoting *PSC*, 355 F.3d at 1360). Yet such a generic reference is all that Akimoto makes with respect to pemetrexed.

In addition, as the district court recognized, even if Akimoto somehow disclosed pemetrexed, it does not disclose tromethamine at all—not on its own and not as pemetrexed ditromethamine. *See* Appx14. All agree that Akimoto does not specifically identify tromethamine as a pharmaceutically acceptable salt. Appx4539-4540, Appx4637. Instead, Akimoto lists several *categories* of salts that could be used with the compounds covered by the patent, along with several examples for each category:

> Such salts are produced by the known methods, and exemplified by the salts of pharmaceutically acceptable bases or acids and quaternary salts. Salts of bases include salts of alkali metals, alkali earth metals, non-toxic metals, ammonium and substituted ammonium, such as sodium, potassium, lithium calcium, magnesium, aluminum, zinc, ammonium, thimethylammonium, thiethylammonium, thiethanol-ammonium, pyridinium and substituted pyridinium. Salts of acids and boric acid, and salts of organic acids

> such as oxalic acid, tartaric acid, acetic acid, trifluoroacetic acid, methanesulfonic acid and camphorsulfonic acid. Quaternary salts include salts of methyl bromid, methyl iodide, methyl methanesulfonate, methyl benzensuflonate and methyl p-toluenesulfonate.

Appx7939. It is undisputed that many of the items on this list are themselves families of compounds, meaning that this list represents a large and unquantifiable roster of potential salt agents. Appx4539-4540. Within this list is a reference to "substituted ammonium," of which tromethamine is one (but not one of the exemplary such substances listed in the patent). DRL seizes on this inclusion of "substituted ammonium," arguing that it necessarily discloses the tromethamine salt form. Br. 11, 60-61. That is wrong, and the district court correctly rejected it. Appx14. As Lilly's expert explained, "substituted ammonium" is itself a generic reference, encompassing a large number of individual salt forming agents, of which tromethamine is but one. Appx4539-4540. That is insufficient to constitute a disclosure of tromethamine for purposes of disclosure-dedication. *SanDisk*, 695 F.3d at 1363-64. And it means that DRL's arguments hinge on an argument that a genus, not merely of thousands of antifolates, but *hundreds of thousands* of antifolate salts that are purportedly suggested by a combination of two genuses, one of antifolates and one of salts, discloses pemetrexed ditromethamine. *See* Appx4539.

DRL attempts to narrow the category of "substituted ammonium" salts in Akimoto by arguing that the POSA would focus only on those that were "FDA-approved." Br. 60-61. Akimoto contains no such limit, and the district court correctly rejected this approach. Appx14. Contrary to DRL's argument, Akimoto specifically identifies "trimethylammonium, triethylammonium, and triethanolammonium" as three preferred examples of substituted ammonium salts to be used with the compounds in Akimoto, but *none* of these is FDA-approved. Appx4440, Appx4715-4716, Appx7939, Appx8033. The notion that the POSA would read into Akimoto's broad disclosure a disclosure of tromethamine specifically because it was FDA-approved is just a results-driven attempt to find a disclosure where there is none.[7]

None of the district court's findings regarding these disclosures are erroneous. Without a specific disclosure of either pemetrexed or tromethamine, there is no basis for DRL's assertion that pemetrexed ditromethamine is disclosed. That pemetrexed ditromethamine is

[7] For many of the same reasons, the other five references do not sufficiently disclose tromethamine. Like Akimoto, they list salt-forming cations including, among others, "substituted ammonium" salts, a generic reference to a family of compounds. And when they identify specific examples of ammonium salts, tromethamine is never listed. *See* Appx4720-4728, Appx7953, Appx7965, Appx7970-7971, Appx7082, Appx8025.

encompassed by these references does not mean that is *disclosed*, especially when it is merely one among the hundreds of thousands of possibilities within Akimoto's generic disclosure, and is entirely absent from the other references. As a matter of law, this cannot support application of the disclosure-dedication rule. *SanDisk*, 695 F.3d at 1366; *PSC*, 355 F.3d at 1360.

C. Pemetrexed Ditromethamine Is Not Disclosed as an Alternative to Pemetrexed Disodium.

Even if DRL could cobble together a disclosure of pemetrexed ditromethamine, its argument would still fail for the independent reason that the '209 patent does not disclose pemetrexed ditromethamine *as an alternative* to pemetrexed disodium. *See Pfizer*, 429 F.3d at 1379. The paragraph of the specification that cites Akimoto, the Taylor patents, and the EPO application lists those references as examples of alternative antifolates. Appx49. The '209 patent defines "antifolate" by reference to a compound's ability to inhibit "at least one key folate-requiring enzyme." Appx49. Under this definition, the POSA would understand that pemetrexed ditromethamine and pemetrexed disodium are the *same* antifolate, not different ones, as it is undisputed that pemetrexed, separated from its counter-ion, is what inhibits an enzyme. Appx4390-4392, Appx4709-4710. There is no basis for reading the cited references as disclosing other pemetrexed salts as alternatives to

pemetrexed disodium; rather, the various compounds and references listed, including Akimoto, suggest that other active antifolate moieties are alternatives to pemetrexed. *See* Appx49, Appx7939-7949, Appx4540-4541. Thus, DRL's argument fails for the additional reason that the '209 patent does not disclose pemetrexed ditromethamine as an alternative to pemetrexed disodium.

D. DRL's Other Asserted Errors Are Baseless.

1. DRL faults the district court at multiple points for allegedly imposing a "§ 112 requirement" in evaluating the question of disclosure-dedication. Br. 57, 61, 62-63, 65-66. But DRL misconstrues both the legal standard and what the district court did. The district court did not expressly or implicitly decline to find a disclosure of pemetrexed ditromethamine based on § 112 standards. Rather, it applied this Court's decision in *SanDisk*, and asked whether the disclosure was specific enough from the perspective of the POSA. Appx13-14, Appx37-39. The district court found overwhelming evidence that pemetrexed ditromethamine was simply not disclosed at all—at best, it was one of hundreds of thousands of compounds that fell within a broad generic disclosure in a reference cited by the patent rather than in the patent itself, which falls far short of the specific disclosure *SanDisk* requires.

2. DRL also argues that the '209 patent discloses pemetrexed ditromethamine because "a skilled artisan with the '209 patent in hand" would find pemetrexed and tromethamine in Akimoto. Br. 59-61. According to DRL, Akimoto's vast genus of antifolates is not a problem because the POSA would know to go looking for pemetrexed, would select tromethamine by restricting Akimoto to FDA-approved salt forms, and would thus necessarily reach pemetrexed ditromethamine. Br. 59-61. And by failing to inquire as to whether the POSA would identify pemetrexed ditromethamine within Akimoto's generic disclosure, DRL argues, the district court "misapprehend[ed] the record and fail[ed] to give legally required weight to the perspective of a person of ordinary skill in the art." Br. 67. DRL is effectively arguing that an alternative can be deemed to be disclosed in the specification of a patent—even if it is not mentioned anywhere—if the alternative would be obvious to a competitor in light of the specification and the prior art cited therein.

That is not the law. As this Court has recognized, the question is *not* whether the POSA "ultimately could employ the disclosures of the patent to implement a purported equivalent," but rather whether the specification "actually disclos[es]" the equivalent to the POSA as an alternative to a claim

limitation. *SanDisk*, 695 F.3d at 1364; *see PSC*, 355 F.3d at 1360. The only witness with the perspective of the POSA—the only oncologist—was Lilly's expert Dr. Chabner, who testified that the POSA would not have understood pemetrexed ditromethamine to be disclosed as an alternative. Appx4437-4439. Moreover, contrary to DRL's assertion, the district court made clear that it was evaluating disclosure-dedication from the perspective of the POSA. Appx13-14, Appx37-39.

DRL's evidence does nothing to even establish that Akimoto *actually discloses* pemetrexed ditromethamine for purposes of the disclosure-dedication rule. It certainly cannot establish that the '209 patent, which merely cites Akimoto, discloses pemetrexed ditromethamine.

III. THE DISTRICT COURT'S INFRINGEMENT FINDING WAS NOT CLEARLY ERRONEOUS.

Finally, DRL turns to the merits of whether using its product would infringe the asserted claims of the '209 patent under the doctrine of equivalents. Br. 70-74. This is a fact question that the district court decided in Lilly's favor. Appx15-19. DRL nevertheless asserts that the court erred in evaluating equivalence by "disregard[ing] key claim language" and treating the claims of the '209 patent as being directed to a method of treating cancer. Br. 70. The district court made no such error.

1. In evaluating equivalence, the Supreme Court has made clear that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention[.]" *Warner-Jenkinson*, 520 U.S. at 24. An equivalent is compared against the patent on an element-by-element basis, not against the invention as a whole. *Id.* DRL's product is thus equivalent if it "contain[s] elements identical or equivalent to each claimed element of the patented invention." *Id.* at 40. In making this determination, the district court is obligated to consider "the context of the patent, the prior art, and the particular circumstances of the case." *Id.* at 24.

The district court faithfully followed the law. After a bench trial, the court concluded that, in the context of the claimed methods, administering pemetrexed ditromethamine is insubstantially different from administering pemetrexed disodium. The district court found that "pemetrexed ditromethamine treats the patient's cancer in exactly the same way as pemetrexed disodium" because both dissolve completely in solution prior to administration, both dissociate completely when dissolved into "free pemetrexed and therapeutically irrelevant counterions," and both of the resulting solutions are "identical" for purposes relevant to the asserted claims. Appx17-18. The district court also found that the chemical differences DRL

asserts between pemetrexed ditromethamine and pemetrexed disodium—solubility, stability, pH, and buffering capacity—"are irrelevant in the context of the claimed method." Appx18. Accordingly, the court correctly found that administering pemetrexed ditromethamine and administering pemetrexed disodium are insubstantially different. Appx17-18.

2. DRL takes exception to the district court's finding—part of its equivalence analysis—that the '209 patent is directed to a "claimed method of treatment" and that the "relevant context" of the claims "relates to medical treatment." Br. 70-74; *see* Appx17-19. Seizing on this choice of language, DRL asserts that the claims literally recite a method of administering pemetrexed disodium, not a method of treatment, and therefore the district court erred by inquiring as to how pemetrexed ditromethamine and pemetrexed disodium achieve the patent's goal of mitigating "toxicity in patients receiving chemotherapeutic treatment." Br. 70-74; *see* Appx10-11. Relatedly, DRL claims that the court erred in focusing on the perspective of the medical oncologist who actually treats patients and thus actually practices the claims. Br. 72; *see* Appx15-16. Instead, DRL argues that the focus of the analysis should have been on chemical differences between pemetrexed disodium and pemetrexed ditromethamine as solid compounds, not on whether they are

equivalent in the context of treating cancer patients.

DRL is ignoring that the claims are not simply directed to a method for administering pemetrexed disodium. Rather, they are directed to methods for administering pemetrexed disodium *to a patient who needs that chemotherapeutic treatment.* *See* Appx52-53.[8] In substance, as the district court found, the asserted claims are directed to ways of treating cancer patients with pemetrexed chemotherapy, and there is no legal rule that they must include the magic words "method of treatment" in order to do so.

For instance, claim 1 recites:

> 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*[.]

Appx52 (emphasis added). That this claim is directed to the medical activity of giving pemetrexed disodium to cancer patients to treat their cancer is established by both the reference to a "patient in need" of pemetrexed and the

[8] DRL's own expert recognized that the goal of administering pemetrexed disodium is to "provide free pemetrexed in an amount sufficient to and capable of reducing tumor growth," Appx4681, and the result of administering pemetrexed disodium in the context of the claimed methods is to treat cancer, Appx4700.

requirement that a patient must receive "an effective amount" of pemetrexed disodium.

The other independent claim, Claim 12, likewise makes explicit the relevant context of treatment. It recites "[a]n improved method for administering pemetrexed disodium to a patient in need of *chemotherapeutic treatment*." Appx53 (emphasis added), *see* Appx4382-4383. Thus, again, the claims are clearly directed at administering pemetrexed disodium to a cancer patient to achieve a therapeutic result.[9]

Moreover, the overall context of the claims shows that the district court was correct. The claims recite administration of pemetrexed disodium after pretreatment with folic acid and vitamin B_{12}. Appx52-53; *see* Appx4382-4383, Appx4398-4399. As Dr. Chabner explained, this vitamin pretreatment is used to ameliorate the toxicities that a patient can experience with pemetrexed treatment without eliminating its efficacy. Appx4282-4283, Appx4390-4399;

[9] DRL suggests that the '209 patent cannot claim of methods of treatment because the examiner rejected claims in a priority application reciting a "method of inhibiting tumor growth" for lack of enablement under § 112. Br. 18, 71-72. That rejection says nothing about Lilly's ability to claim the combined administration of folic acid, vitamin B_{12}, and pemetrexed disodium as an improved method of treatment. And it does nothing to undermine the fact that the examiner approved claims that referred to administering a chemotherapy agent to patients in need of chemotherapeutic treatment.

Teva, 845 F.3d at 1362. Accordingly, claim 1 requires "administering an effective amount" of folic acid and a methylmalonic acid lowering agent (which includes vitamin B_{12}), and claim 12 recites an improved method that includes the administration of folic acid, vitamin B_{12}, and pemetrexed disodium. Appx52-53. Improving the safety of chemotherapy is an advance in the field of medical oncology, not pharmaceutical chemistry. The district court did not err by inquiring whether administering pemetrexed ditromethamine and administering pemetrexed disodium are insubstantially different medical treatments. That is precisely "the context of the patent" that *Warner-Jenkinson* directs courts to consider. 520 U.S. at 24.

DRL's argument is further undermined by the fact that the compound pemetrexed disodium, the procedure for getting pemetrexed into solution, and the procedure for administering a solution of pemetrexed disodium were all known in the prior art. Appx4398-4399, Appx4686-4687; *see Warner-Jenkinson*, 520 U.S. at 24 (directing courts to consider the "prior art"). This is confirmed by claim 12, a "Jepson-style" claim in which the preamble defines the "elements or steps of the claimed invention which are conventional or known." *Rowe v. Dror*, 112 F.3d 473, 479 (Fed. Cir. 1997) (quoting 37 C.F.R. § 1.75(e)). Because "administering pemetrexed disodium" appears in the

preamble, it was known in the art at the time of the invention. *See id.* DRL has not and cannot point to anything novel about the act of administering pemetrexed disodium *per se*. The novel method, rather, is a three-step treatment regimen in which folic acid, vitamin B_{12}, and pemetrexed disodium are administered to patients on a particular schedule. Appx52-53, Appx4382, Appx4398-4399. That is what the claims in substance are about, and the district court was correct to apply this context in deciding equivalence.[10]

3. Even assuming, *arguendo*, that the claims were limited to a method of administering pemetrexed disodium as DRL suggests, the district court was still correct to conclude that the differences DRL identifies in this appeal—solubility, stability, pH, and buffering capacity—are not relevant and have no impact on the equivalence analysis. *See* Appx18-19. DRL does not dispute that that pemetrexed ditromethamine and pemetrexed disodium must be completely dissolved in solution prior to administration, that both are

[10] DRL argues that this interpretation of the claims means that "*any* composition that treats cancer in a patient as pemetrexed disodium does" will infringe. Br. 72. It is unclear what DRL means by "as pemetrexed disodium does" or what level of generality it envisions. If what DRL is saying is that Lilly could pursue infringement against compositions that are equivalent to pemetrexed disodium in the context of the claims, that is exactly what the doctrine of equivalents allows. There is nothing controversial or interesting about DRL's observation, and it provides no basis for error.

administered as liquids, that the same active pharmaceutical moiety is administered in each case, and that the dissociated counter-ions—sodium or tromethamine—are therapeutically inactive. Appx4384-4398, Appx4520-4526, Appx4684-4686, Appx4709-4710. To the extent there are comparative differences in the solubility, stability, pH, and buffering capacity, it is undisputed that those differences have *no impact* on how pemetrexed ditromethamine and pemetrexed disodium are administered. Appx4429-4434, Appx4499-4501, Appx4526-4532, Appx4706-4709. Both salt forms supply dissociated pemetrexed the same way. The district court was thus correct to recognize that in the context of liquid administration, both products are "identical" after being prepared for administration. Appx18-19.

DRL, for its part, makes no effort to explain how these difference are relevant in the context of a liquid administration, stating only that the differences must receive "their legally required due." Br. 74. DRL does not explain, for example, how the features of pemetrexed ditromethamine it cites change the equivalence analysis based on the record in this case.

Ultimately, the record establishes that the district court gave these differences proper consideration and rejected them in concluding that the administration of pemetrexed ditromethamine is equivalent to the

administration of pemetrexed disodium. To do so was not clearly erroneous. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1352 (Fed. Cir. 2003) (an identified difference must "actually affect[a] property . . . relevant to the claim at hand").

CONCLUSION

For these reasons, the decision of the district court should be affirmed.

Respectfully submitted,

DECEMBER 3, 2018

/s/ Adam L. Perlman

ADAM L. PERLMAN
DOV P. GROSSMAN
DAVID M. KRINSKY
GALINA I. FOMENKOVA
CHARLES L. MCCLOUD
ANDREW P. LEMENS
WILLIAMS & CONNOLLY LLP
725 Twelfth Street, N.W.
Washington, DC 20005
(202) 434-5000

JAMES P. LEEDS
ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-1667

Attorneys for Plaintiff-Appellee

CERTIFICATE OF SERVICE

I, Adam L. Perlman, hereby certify that on December 3, 2018, I caused the foregoing document to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification to the registered attorneys of record that the document has been filed and is available for viewing and downloading.

DECEMBER 3, 2018

/s/ *Adam L. Perlman*
ADAM L. PERLMAN

Attorney for Plaintiff-Appellee

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32 and Federal Circuit Rule 32. The brief contains 13,936 words, excluding the parts of the brief exempted by Federal Circuit Rule 32(b) and Federal Rule of Appellate Procedure 32(f).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point CenturyExpd BT.

DECEMBER 3, 2018

/s/ Adam L. Perlman
ADAM L. PERLMAN

Attorney for Plaintiff-Appellee