No. 2024-2325

United States Court of Appeals for the Federal Circuit

WYETH LLC,

Plaintiff-Appellant,

v.

ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB,

Defendants-Appellants.

Appeal from District Court for the District of Delaware,
Case No. 21-cv-01338-MFK, Judge Matthew F. Kennelly

OPENING BRIEF OF APPELLANT WYETH LLC

Anthony M. Insogna
Meredith A. Stewart
Daniele San Román
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, California
(858) 314-1130

Jason G. Winchester
JONES DAY
110 North Wacker Drive, Suite 4800
Chicago, IL 60606
(312) 269-4373

Gasper J. LaRosa
JONES DAY
250 Vesey Street
New York, New York
(212) 326-7885

Jennifer L. Swize
JONES DAY
51 Louisiana Avenue, N.W.
Washington, DC 20001
(202) 879-3939

Matthew J. Rubenstein
JONES DAY
90 South Seventh St., Suite 4950
Minneapolis MN, 55402
(612) 217-8800

Daniel Paul Johnson
JONES DAY
500 Grant Street, Suite 4500
Pittsburgh, PA 15217
(412) 394-7217

Counsel for Appellant Wyeth LLC

CLAIMS AT ISSUE

Four claims from two different patents are at issue: claim 1 of U.S. Patent No. 10,596,162 (the '162 patent) and claims 1, 3, and 9 of U.S. Patent No. 10,603,314 (the '314 patent). The first claim of each patent is representative:

U.S. Patent No. 10,596,162

> 1. A method of treating gefitinib and/or erlotinib resistant non-small cell lung cancer having a T790M mutation in SEQ ID NO: 1 in a patient, comprising administering daily to the patient having gefitinib and/or erlotinib resistant non-small cell lung cancer having a T790M mutation in SEQ ID NO: 1 a pharmaceutical composition comprising a unit dosage of 2-500 mg of an irreversible EGFR inhibitor that covalently binds to cysteine 773 of the catalytic domain within the SEQ ID NO: 1 having a T790M mutation; wherein the irreversible EGFR inhibitor is not CL-387,785.

U.S. Patent No. 10,603,314

> 1. A method for treating gefitinib and/or erlotinib resistant non-small cell lung cancer in a patient in need thereof, comprising administering daily to the patient having gefitinib and/or erlotinib resistant non-small cell lung cancer a pharmaceutical composition comprising a unit dosage of an irreversible epidermal growth factor receptor (EGFR) inhibitor that covalently binds to cysteine 773 residue in the ligand-binding pocket of EGFR or cysteine 805 residue in the ligand binding pocket of erb-B2.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2024-2325

Short Case Caption Wyeth LLC v. AstraZeneca Pharmaceuticals LP

Filing Party/Entity Wyeth LLC

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
4. Please do not duplicate entries within Section 5.
5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 12/18/2024

Signature: /s/ Jennifer Swize

Name: Jennifer Swize

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Wyeth LLC		Pfizer Inc.
Please see attached for related disclosure.		

☑ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☑ Additional pages attached

Please see attached.		

5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☑ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

FORM 9. Certificate of Interest – Parts 1–3.
(Attachment)

1. Represented Entities: For the purpose of assisting the Court in assessing whether recusal by a judge is necessary or appropriate (*see* Fed. Cir. Rule 47.4(a)), Wyeth also notes that Puma Biotechnology, Inc. ("Puma") was a party below and maintains an interest in this dispute.

2. Real Party in Interest: N/A

3. Parent Corporations and Stockholders: None (Puma has no parent corporation, and no publicly held corporation owns ten percent or more of its stock.)

FORM 9. Certificate of Interest – Part 4. Legal Representatives
(Attachment)

The following firms, partners, and associates also appeared for Wyeth LLC in the originating proceedings.

JONES DAY
Steven N. Geise
Miguel A. Alvarez
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
(858) 314-1200

Lisamarie LoGiudice
250 Vesey Street
New York, NY 10281
(212) 326-3939

Bethany K. Biesenthal
John M. Michalik
Michelle B. Smit
Jeffrey S. Messing
110 N. Wacker Drive, Suite 4800
Chicago, IL 60606
(312) 782-3939

Alexis Adian Smith
555 South Flower Street, Fiftieth Floor
Los Angeles, CA 90071
(213) 243-1542

Shehla Wynne (*no longer affiliated*)
51 Louisiana Avenue, N.W.
Washington, DC 20001
(202) 879-3939

John C. Evans
North Point
901 Lakeside Avenue
Cleveland, Ohio 44114
(216) 586-3939

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld
Rodger D. Smith II
Megan E. Dellinger
Travis J. Murray
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200

WILKIE FARR & GALLAGHER LLP
Sara T. Horton
Ren-How Harn
Henry C. Thomas
300 North LaSalle
Chicago, IL 60654-3406
(312) 728-9040

The following firms, partners, and associates appeared for Puma Biotechnology, Inc. in the originating proceedings.

JONES DAY
Anthony M. Insogna
Steven N. Geise
Meredith A. Stewart
Daniele San Román
Miguel A. Alvarez
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
(858) 314-1200

Gasper J. LaRosa
Lisamarie LoGiudice
250 Vesey Street
New York, NY 10281
(212) 326-3939

Bethany K. Biesenthal
Jason G. Winchester
John M. Michalik
Michelle B. Smit
Jeffrey S. Messing
110 N. Wacker Drive, Suite 4800
Chicago, IL 60606
(312) 782-3939

Alexis Adian Smith
555 South Flower Street, Fiftieth Floor
Los Angeles, CA 90071
(213) 243-1542

Jennifer Swize
Shehla Wynne (*no longer affiliated*)
51 Louisiana Avenue, N.W.
Washington, DC 20001
(202) 879-3939

John C. Evans
North Point, 901 Lakeside Avenue
Cleveland, Ohio 44114
(216) 586-3939

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld
Rodger D. Smith II
Megan E. Dellinger
Travis J. Murray
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200

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TABLE OF ABBREVIATIONS

'162 patent	U.S. Patent No. 10,596,162
'314 patent	U.S. Patent No. 10,603,314
Allen	Allen et al., *Potential Benefits of the Irreversible Pan-erbB Inhibitor, CI-1033, in the Treatment of Breast Cancer*, 29 Seminars in Oncology (Iss. 3 Supp. 11) 11-21 (2002)
Agus	Agus, *Method of Treating Cancer Using Kinase Inhibitors*, WO 03/103676 A2 (2003)
Court	U.S. Court of Appeals for the Federal Circuit
district court, or court	U.S. District Court for the District of Delaware, Judge Matthew F. Kennelly (sitting by designation)
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
Greenberger	Greenberger et al., 11th NCI-EORTC-AACR Symposium on New Drugs in Cancer Therapy, Abstract 388 (2000)
Hidalgo	Hidalgo et al., *Phase 1 trial of EKB-569, an irreversible inhibitor of the epidermal growth factor receptor (EGFR), in patients with advanced solid tumors*, ASCO Annual Meeting Proceedings, 21:17a; Abstract 65 (2002)
JMOL	judgment as a matter of law
Kwak	Kwak et al., *Irreversible Inhibitors of the EGF Receptor may Circumvent Acquired Resistance to Gefitinib*, 102 Proceedings of the National Academy of Sciences of the United States of America (Iss. 21) 7665-70 (2005)
Lynch	Lynch et al., *Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small Cell Lung Cancer to Gefitinib*, 350 New England J. of Med. (Iss. 21) 2129-39 (2004)

NSCLC	non-small cell lung cancer
POSA	person of skill in the art, or skilled artisan
Rabindran	Rabindran, et al, *Antitumor Activity of HKI-272, an Orally Active, Irreversible Inhibitor of the HER-2 Tyrosine Kinase*, 64 Cancer Resch. (Iss. 11) 3958-65 (2004)
Smaill	Smaill et al., *Tyrosine Kinase Inhibitors. 15. 4-(Phenylamino)quinazoline and 4-(Phenylamino)pyrido[d]pyrimidine Acrylamides as Irreversible Inhibitors of the ATP Binding Site of the Epidermal Growth Factor Receptor*, 42 J. Med. Chem (Iss. 10) 1803-15 (1999)
Wissner	Wissner et al., *Synthesis and Structure-Activity Relationships of 6,7-Disubstituted 4-Anilinoquinoline-3-Carbonitriles. The Design of an Orally Active, Irreversible Inhibitor of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor (EGFR) and the Human Epidermal Growth Factor Receptor-2 (HER-2)*, 46 J. Med. Chem. (Iss. 1) 49-63 (2003).

STATEMENT OF RELATED CASES

Wyeth is not aware of any case pending in this or any court or agency within the meaning of Rule 47.5 that will directly affect the Court's decision in this case or that could be affected by the Court's decision.

STATEMENT OF JURISDICTION

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). The jury rendered a verdict for Wyeth on May 17, 2024. But on August 14, 2024, the court granted AstraZeneca's Rule 50(b) motion and entered final judgment for AstraZeneca. This appeal, noticed September 12, 2024, is timely. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

INTRODUCTION

This appeal centers on the district court's post-verdict change of construction of "unit dosage"—a change that was substantively incorrect, evidentiarily insufficient to support the court's JMOL ruling, and procedurally too late. The claims recite a method for treating lung cancer by administering a "unit dosage" of certain compounds (irreversible inhibitors of a protein called EGFR). Through trial, the court was clear: a "unit dosage" takes its definition from the specification, which states that a unit dose is calculated to produce the desired therapeutic effect, i.e., inhibiting EGFR and killing cancer cells. The court was likewise clear that this definition requires no particular level of safety or proof of passing standards for clinical trials. The court adopted this meaning at *Markman*, adhered to it in pretrial rulings, and again adhered to it at trial, instructing the jury that "unit dosage" refers, as relevant here, to "material calculated to produce the desired therapeutic effect" and "does not require clinical efficacy."[1] Using that construction, the jury returned a verdict of infringement, found that AstraZeneca failed to prove invalidity, and awarded damages.

[1] Appx2436-37 (*Markman* order construing "unit dosage" to mean, in relevant part, "calculated to produce the desired therapeutic effect" per the specification's definition); Appx17315-16 (12:5-13:9) (reiterating before trial that the claims do not require proof that the dosage is "safe and efficacious or effective"); Appx141-42 (final jury instructions stating "[t]his claim term does not require clinical efficacy").

After the verdict, the court rejected AstraZeneca's JMOL arguments under the governing construction and held that AstraZeneca *failed* to clearly and convincingly prove the patents do not enable or describe a "unit dosage" yielding the desired "therapeutic effect." The court should have stopped there. It did not.

Instead, it tested the verdict against a new post-verdict construction that AstraZeneca never requested and that contradicted the court's previously consistent construction. Without hearing oral argument, the court granted JMOL that the claims do not enable or describe a "unit dosage" because, in the court's newly announced view, that term *does* require safety and clinical efficacy in that it must not "fatally poison a patient" or be "unduly toxic."

The court was wrong. First and foremost, that new, post-verdict construction contradicts decades of Federal Circuit law. As the court previously recognized, the claims require *no* particular level of safety, and nowhere incorporate other clinical or regulatory standards. By imposing such requirements, the court contravened this Court's directive that, "[a]bsent incorporation of safety and efficacy requirements in the claims," such questions are "not before us" and are instead "the purview of the FDA." *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1369 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 873 (2024). If the court's construction were to stand, the resulting burdens of clinical testing to enable and describe method-of-treatment claims "would prevent many companies from obtaining patent protection

on promising … potential cures." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). Thus, on the legal merits of the court's post-verdict reconstruction alone, JMOL should be reversed and the verdict reinstated.

Plenty of other reasons compel the same relief. For instance, even accepting the court's post-verdict reconstruction, the trial evidence would not require an invalidity finding. The court believed that determining dosages that avoid lethality and undue toxicity would require undue experimentation. But the evidence shows no such thing. AstraZeneca never even pursued "lethality" at trial, and for good reason—as the record shows, irreversible EGFR inhibitors were known in the art and had previously been administered to and tolerated by patients in similar contexts. The evidence also fails to support JMOL based on "undue toxicity" concerns. Rather, the record shows that irreversible EGFR inhibitors carry risks of ordinary and expected side effects—gastrointestinal issues, skin rash, and the like—and that such risk would not preclude the ability to practice the claims. Instead, as with many drugs, given an opportunity to prolong life, doctors readily suggest, and patients readily agree to, treatment notwithstanding such side effects.

The court also procedurally erred by re-construing the claims post-verdict. By reading the claims to require the skilled artisan to be able to calculate a unit dosage within certain safety constraints, the court adopted a new limitation it had consistently rejected. JMOL is too late for such a change.

At the least, the court's errors render the result fundamentally unfair and necessitate further proceedings. Had the court adopted its post-verdict reconstruction at the proper time, it would still have been incorrect, but Wyeth could have developed additional safety evidence. At minimum, a remand for that opportunity is needed.

This appeal also presents a second issue—one of first impression for this Court: whether pre-patent-issuance provisional rights under 35 U.S.C. § 154(d) include induced infringement (the type of infringement AstraZeneca committed). The district court held that § 154(d) does not apply to induced infringement because it does not specifically mention induced infringement. In doing so, the court failed to read the statute as a whole and to credit its purpose to protect patentees from pre-issuance infringement, regardless of type. On remand, Wyeth should be permitted to pursue its § 154(d) pre-issuance damages claim.

STATEMENT OF THE ISSUES

1. Whether the district court erred in granting JMOL based on its conclusions that the skilled artisan "would have to undertake undue experimentation to find a 'unit dosage' that would not fatally poison a patient," Appx57, and that the patents did not adequately describe a safe, "administrable unit dosage—if any—for different compounds covered by the asserted claims," Appx67, where:

(a) as in *United Therapeutics Corp. v. Liquidia Technologies, Inc.*, 74 F.4th 1360 (Fed. Cir. 2023), the claims are directed to a "therapeutic effect" and do not claim any particular patient safety standard (e.g., non-lethality);

(b) even under the court's post-trial reconstruction, AstraZeneca never advanced a fatal dosages argument, and the evidence showed that patients tolerated unit dosage administration of relevant compounds consistent with side effects common to all EGFR inhibitors (e.g., gastrointestinal and dermatologic issues), including AstraZeneca's own product, Tagrisso; and

(c) the court's post-verdict reconstruction departed from its *Markman*/trial construction that the claims do not require safety or other endpoints that might be relevant to clinical trials or FDA approval.

2. Whether the district court erred in granting summary judgment of no pre-issuance damages based on its statutory interpretation that pre-issuance patent rights under 35 U.S.C. § 154(d) do not protect against induced infringement.

STATEMENT OF THE CASE

A. The Claimed Inventions

The inventors discovered a new method for treating drug-resistant non-small cell lung cancer ("NSCLC"). That method uses irreversible inhibitors to disrupt epidermal growth factor receptor ("EGFR") pathways and thereby kill cancer cells in patients.

1. Existing NSCLC Treatments Were Ineffective for Most Patients

NSCLC is a leading cause of cancer death. Appx204 (1:45-46); Appx17352 (157:24-158:10). Late-stage NSCLC is particularly difficult to treat by conventional means because it often spreads outside the lungs and becomes inoperable. Appx17352 (158:11-159:7). Since the early 2000s, targeted drug therapies have been a focus for late-stage treatment. Appx204 (1:47-52); Appx17352 (158:21-159:13); Appx17386 (293:6-15). These novel therapies—including the patented discovery here—target specific cellular features underlying a patient's cancer to impede the disease's progress. *E.g.*, Appx204 (1:47-52); Appx17353 (161:22-162:8); Appx17388 (299:23-300:17).

NSCLC is associated with overactivity of EGFR, a protein involved in cell division.[2] Appx17352 (159:18-160:5). Accordingly, early drug therapies for metastatic NSCLC focused on EGFR inhibition. Appx17353 (161:22-162:15). Among these were erlotinib and AstraZeneca's gefitinib product, Iressa, which AstraZeneca began marketing in 2003. Appx17353 (162:9-163:3); Appx17386 (293:16-23); Appx17538 (901:8-902:6). These compounds bind to a specific part of EGFR, preventing it from facilitating cancerous growth. Appx17353 (161:22-162:8). Gefitinib and erlotinib are "reversible" EGFR inhibitors because they bond to EGFR non-covalently. Those non-covalent bonds eventually break, eliminating the inhibitor's therapeutic effect. Appx17353 (162:9-20).[3]

Gefitinib treatment had two significant limitations. Appx205 (3:19-23). ***First***, many NSCLC patients did not respond to gefitinib, and doctors could not predict which patients would respond. Appx17386 (293:16-23). ***Second***, even responders developed resistance to gefitinib, Appx17387 (295:15-296:10); on average, gefitinib treatment worked to extend the life of responsive, metastatic

[2] EGFR, which is a member of the erbB family of receptors, is also called "EGF-R," "erbB-1," and "HER1." *E.g.*, Appx204 (1:64-2:12, 2:61-62); Appx39612.

[3] For ease of reference, because any differences between gefitinib and erlotinib are immaterial for purposes of this appeal, the remainder of this brief refers only to gefitinib treatments and resistance. *E.g.*, Appx17353 (162:16-22) (Wyeth's expert, Dr. Weiss, observing no difference between "what those compounds are and how they operate that would affect [his] analysis").

NSCLC patients for only nine months, Appx17354 (165:15-25); *see also* Appx206 (6:31-35).

2. After Discovering That Gefitinib Responders Have Specific EGFR Mutations, the Inventors Discovered How to Treat Gefitinib Resistance Using Irreversible Inhibitors

The patents' inventors, Dr. Daniel Haber and his team at Massachusetts General Hospital and Wyeth, made key discoveries related to gefitinib's limitations. They ultimately invented a novel method for treating gefitinib resistance using irreversible EGFR inhibitors.

First, Dr. Haber and his team discovered why certain patients did not respond to gefitinib. Appx17386 (293:24-294:9); Appx17353 (163:10-24). They found that only patients with mutations in EGFR exons 19 and 21—called "sensitizing mutations"—respond to gefitinib. Appx20318-21; Appx17353 (163:7-20); Appx17356 (176:15-21). In these patients, gefitinib therapy "melt[ed] away" NSCLC tumors. Appx17386 (293:24-294:5). The inventors reported this discovery in the "landmark" Lynch paper (named for the first-listed inventor on the publication). Appx17388 (299:23-300:17); *see* Appx20312; Appx17386 (292:22-294:9).

Second, Dr. Haber and his team discovered a solution to gefitinib resistance: a treatment method using "irreversible" EGFR tyrosine kinase inhibitors. Appx17354 (167:7-168:22). The inventors specifically investigated the T790M

"resistance mutation," which is responsible for most failures of gefitinib therapy in patients with sensitizing mutations. Appx17354 (166:14-167:9). Irreversible inhibitors, the inventors found, suppress EGFR and kill cancer cells even in patients whose cancers possessed the T790M resistance mutation. Appx205 (3:43-46); *see* Appx207 (7:10-23); Appx17388-89 (302:20-303:18).

Dr. Haber and his team published this discovery in the Kwak paper (again named for the first-listed inventor). Appx18197; Appx17390 (309:19-310:3). The inventors filed provisional patent applications on February 3, 2005, and April 15, 2005. Appx176; Appx223. After a comprehensive examination, the Patent Office issued the '314 patent and the '162 patent—the patents-in-suit. Both patents claim methods of using irreversible inhibitors to treat gefitinib-resistant NSCLC.

3. The Class of Irreversible Inhibitors Used in the Claims Was Familiar to the Skilled Artisan

The inventors discovered a method of treatment using irreversible inhibitors—not irreversible inhibitors themselves. Both reversible and irreversible inhibitors were known to the skilled artisan at the time of the invention.[4] Experts in

[4] A "skilled artisan" would have a "doctoral degree in a discipline such as organic or medicinal chemistry … and at least three years of practical experience in drug discovery and development, including for cancers that may benefit from kinase inhibition …." Appx17357 (177:24-178:16) (testimony of Wyeth's expert, Dr. Weiss). He or she "would work together with one or more team members with experience developing cancer treatments" such as "molecular biologists, geneticists,

the field had worked with EGFR inhibitors since the 1990s. *E.g.*, Appx17375 (251:12-16); Appx204 (2:41-46) (discussing a 2002 review of inhibitors "targeting the ErbB family of tyrosine kinase receptors," Appx20294); Appx207 (7:29-36) & Appx210 (13:50-58) (discussing other experiences with EGFR inhibitors). The reversible inhibitors gefitinib and erlotinib, for instance, had been studied in "very large trials … in patients with lung cancer." Appx17386 (293:16-23); *see also* Appx204-05 (2:65-3:18) (discussing these compounds, their features, and their administration).

Similarly, the parties agree that "irreversible EGFR inhibitors were known prior to February 3rd, 2005," the patents' priority date.[5] Appx17438 (501:3-502:10) (also agreeing on specific known compounds); *see also, e.g.*, Appx17475 (648:19-21) (AstraZeneca's expert Dr. Jänne acknowledging the specification's discussion of known irreversible inhibitors). In fact, they were known by the 1990s. Appx17444 (525:6-526:7) (AstraZeneca's expert Dr. Reider acknowledging "examples of irreversible inhibitors that … showed benefit" in "the late 1990s, early

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[and] medicinal chemists … in a multi-disciplinary team …." Appx17357 (178:2-16).

Although AstraZeneca offered a different definition, its witnesses agreed that any differences were immaterial. *See, e.g.*, Appx17454 (566:4-14) (AstraZeneca's expert, Dr. Reider, testifying that his "opinions don't change" depending on which definition is used).

[5] AstraZeneca's argument for a different priority date concerned only one prior-art defense and is thus immaterial on appeal.

2000s"); Appx17415 (410:15-24) (AstraZeneca's witness Dr. Ward noting that "in terms of drug discovery, irreversible inhibitors have been known for quite a while"). The skilled artisan, for instance, would know that irreversible EGFR inhibitors as a class were "very readily" designed, Appx17553-54 (962:17-963:3); Appx17555 (969:14-21), and had certain features that "passed toxicity hurdles," Appx17557 (977:5-978:4); Appx17556-57 (973:23-976:4). Exemplar compounds were available, noted in the specification, and discussed in the literature. Appx17555-56 (969:10-972:1) (discussing the specification and Appx20297 (Table 3)). The patents identify key features of irreversible inhibitors and expressly note the prior art describing them. *E.g.*, Appx17555 (968:18-970:19); Appx17559 (984:20-986:9).

Moreover, by the priority date, irreversible inhibitors had been administered to patients for other purposes. For example, Allen (cited at Appx180) and Hidalgo (cited at Appx179) respectively reported on the administration of irreversible inhibitors CI-1033 and EKB-569 (one of the inventors' preferred embodiments) in daily dosages to patients. In those studies, patients tolerated a variety of doses. *See* Appx39619 (Allen describing "an acceptable side-effect profile at potentially therapeutic doses and schedules" for CI-1033); Appx18499 (Hidalgo reporting that "EKB-569 was generally well tolerated, with an acceptable [pharmacokinetics] and safety profile, and offers a promising targeted approach to the treatment of solid tumors"). No deaths were observed.

Animal studies of irreversible inhibitors before 2005 also helped predict human responses and side effects (also referred to as "toxicities"). Appx17483 (682:15-23); Appx17520 (827:2-7). Greenberger showed that EKB-569 successfully inhibited the growth of human tumor xenografts in mice using daily dosages based on body weight. Appx17798 (the "data, combined with the safety assessment of EKB-569 in animals, suggest that EKB-569 may have utility in the clinic") (noted at Appx207 (7:29-32)); *see also* Appx17845 (Wissner similarly reporting that animal testing helped make EKB-569 a clinical candidate) (cited at Appx191). Rabindran found that irreversible inhibitor HKI-272, another embodiment tested by the inventors and discussed in the patents, "was well tolerated by the animals" receiving daily dosages. Appx17878 (noted at Appx207 (7:34-36)). And Smaill found that six different irreversible inhibitors in animals "all showed significant tumor growth inhibition over a dose range and activity at the highest doses tested without lethality or significant treatment-associated weight loss … indicating acceptable therapeutic indices." Appx17826 (cited at Appx191). All of this information was known to the skilled artisan.

B. AstraZeneca's Infringement and Wyeth's Suit

In the late 2000s, aware of the limitations of its gefitinib product Iressa, AstraZeneca began searching for an NSCLC treatment that could overcome T790M-mediated gefitinib resistance. Appx15027-28 (57:09-59:02); Appx15036 (109:12-

110:07). It launched what it described as a "must-win" project to develop a compound that would target T790M and treat gefitinib resistance. Appx15027 (57:09-57:17); Appx15064 (120:01-120:16); Appx18448.

Consistent with the prior art, AstraZeneca initially focused on developing other *reversible* EGFR inhibitors. But after reviewing the inventors' published patent application and underlying research, AstraZeneca switched focus to irreversible inhibitors. Appx15062-63 (87:18-90:24) (discussing Appx18372 & Appx18376); Appx15057-58 (36:09-36:21). It eventually developed osimertinib, an irreversible EGFR inhibitor that it has marketed as Tagrisso since 2015. Appx15027 (57:09-57:17); Appx17748; Appx17355-56 (172:12-173:19). Tagrisso is administered to patients in daily unit dosages of 40 or 80 milligrams, and it covalently binds to cysteine 773 residue in the ligand-binding pocket of EGFR, just as Wyeth's patents describe and claim. Appx17361-62 (193:12-17, 199:4-13).

After the patents issued, Wyeth sued AstraZeneca for willful, induced infringement based on Tagrisso. Appx324. Wyeth requested a reasonable royalty for both pre- and post-issuance infringement. Appx342.

Claims 1, 3, and 9 of the '314 patent and claim 1 of the '162 patent are at issue. Claim 1 of the '314 patent is generally representative, with particularly relevant phrases italicized:

> A method for treating gefitinib and/or erlotinib resistant non-small cell lung cancer in a patient in need thereof,

> comprising *administering daily to the patient* having gefitinib and/or erlotinib resistant non-small cell lung cancer *a pharmaceutical composition comprising a unit dosage of an irreversible epidermal growth factor receptor (EGFR) inhibitor* that covalently binds to cysteine 773 residue in the ligand-binding pocket of EGFR or cysteine 805 residue in the ligand-binding pocket of erb-B2.

Appx221 (emphases added). Claim 1 of the '162 patent is limited to unit dosages "of 2-500 mg." Appx269 (35:49-57). For purposes of appeal, the patents' specifications are materially the same, and this brief cites the '314 specification as representative. *Compare* Appx175-221 *with* Appx222-269.

C. The District Court Repeatedly Refused to Read a Requirement of Any Particular Level of Safety or Clinical Efficacy into the Claims

Beginning at claim construction, the district court rejected AstraZeneca's argument that the term "unit dosage" requires proof of safety or clinical efficacy. AstraZeneca nevertheless insisted before and during trial on treating the term as though it requires FDA-level safety and effectiveness. The court consistently rejected that view, at least until after the verdict.

1. At *Markman*, the District Court Construed "Unit Dosage" to Require a Therapeutic Effect, Not a "Safe," "Non-Toxic," or FDA-Approved Effect

AstraZeneca pursued a safety and efficacy theory at claim construction. It proposed construing the term "a pharmaceutical composition comprising a unit dosage"—and specifically the term "unit dosage"—using language it borrowed from the specification's definitions of distinct, unclaimed terms. Specifically,

AstraZeneca argued that a "unit dosage" must contain "an effective amount," which AstraZeneca said meant "an amount that results in a beneficial effect for at least a statistically significant fraction of patients considering both its pharmacologic effectiveness and its physiological safety." Appx1127-29; Appx1966-67 (citing the specification's definitions of "effective amount," "effective," and "effectiveness" at Appx207 (8:46-48) & Appx210 (13:14-21)).

The court rejected AstraZeneca's proposal and adopted the specification's explicit definition of "unit dose":

> The term "unit dose" when used in reference to a therapeutic composition of the present invention refers to physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluents; i.e., carrier, or vehicle.

Appx208 (9:33-38); *see* Appx2436-37.[6] The court reasoned that "a patentee's definition of a term controls." Appx2436-37. The court further emphasized that "the patents both defined the term 'effective amount' and used it repeatedly in other parts of the specification," so "the inventors could easily have included the words 'effective amount' in the claim language when defining a 'unit dosage,'" but chose not to do so. Appx2437 (cleaned up). As the court also noted, "neither the preambles

[6] Neither the court nor any party ever claimed any difference existed between "unit dose" and "unit dosage."

nor the claims at issue include the words 'effective amount' or 'therapeutically beneficial,' and the claims use different language—either a 'unit dosage' or 'a unit dosage of 2-500 mg'—to describe the amount of the pharmaceutical composition to administer." Appx2425 (quoting Appx221 (35:56) & Appx269 (35:54)).

2. Before Trial, the District Court Adhered to Its Construction

Despite the court's clear construction, AstraZeneca continued to insist that a "unit dosage" requires a certain level of safety or clinical effectiveness. Accordingly, Wyeth moved *in limine* to exclude evidence related to "FDA approval or clinical trial results" because "[e]fficacy, safety, and FDA approval are not relevant to the claims' validity." Appx11337; *see also* Appx11338 (quoting *United Therapeutics*, 74 F.4th at 1369). AstraZeneca responded that "failure of an irreversible EGFR inhibitor to achieve FDA approval or some other clinical benchmark is probative of … enablement and written description." Appx12980.

The district court, however, agreed with Wyeth as to the claims' scope and largely granted its motion, emphasizing that "[s]afety and efficacy are required for FDA approval, but they are not required for patentability" where, as here, they are not claimed. Appx13293. "Evidence regarding the clinical efficacy of other compounds," the court continued, "might have some probative value if the patent itself required clinical efficacy, but the court ruled during claim construction that it doesn't." Appx13295.

The court permitted evidence related to clinical benchmarks in only a limited respect: to show "whether the patent gives enough guidance to somebody to be able to make a product that is within the patent that's calculated to produce the desired therapeutic effect." Appx17315 (11:19-21). The court appeared influenced by the notion of impossibility—if evidence "show[s] somebody tried what's in the patent and you couldn't come up with it," i.e., that "you can't calculate what would be an effective dose," the court viewed that as relevant to showing "the patent doesn't enable or doesn't have a sufficient written description." Appx17316 (13:3-13:8). But the court emphasized that this evidentiary ruling had no effect on its longstanding construction that the claims do not require proof that the dosage is "safe and efficacious or effective." Appx17315-16 (12:22-13:1) ("[I]t doesn't; I ruled on that.").

3. At Trial, the District Court Instructed the Jury on Its Construction

During trial, AstraZeneca's witnesses repeatedly testified about clinical efficacy and commercialized treatments. *E.g.*, Appx17454 (563:19-23) (Dr. Reider asserting that certain irreversible inhibitors "have limited clinical efficacy"); Appx17472-73 (638:18-639:2) (Dr. Jänne asserting that most drug designs "never make it to the clinic"); Appx17492 (716:22-717:2) (Dr. Taft asserting "to establish a unit dose requires clinical evaluation"). Wyeth therefore sought an instruction that the claims contain no such requirements. The court agreed, noting that "when

somebody says the claim language should include this and I say it shouldn't, that's part of the claim construction." Appx17523 (842:5-16). Thus, the court explicitly told the jury that the term "a pharmaceutical composition comprising unit dosage" "does not require clinical efficacy." Appx17523 (840:13-842:16); Appx140-42.

D. The Verdict

After a five-day trial involving nearly two dozen witnesses, including 10 experts, and almost 200 exhibits, the jury found that AstraZeneca induced infringement (although not willfully), that AstraZeneca failed to prove invalidity, and that Wyeth was entitled to a reasonable royalty of $107.5 million for damages from patent issuance through 2023 (representing a 3.5% implied royalty rate). Appx157; Appx173; Appx16416-17.

The jury's verdict necessarily rejected the premises of AstraZeneca's invalidity theories. The jury heard, for instance, AstraZeneca's expert Dr. Reider assert that "more than billions" of compounds could be designed to practice the claims. Appx17447 (535:15-20). But it also heard Wyeth's expert Dr. Jorgensen explain why that testimony was an "exaggeration" and "irrelevant." Appx17553 (962:9-16) ("A [skilled artisan] would not be thinking in those terms."). The jury thus declined to credit AstraZeneca's "billions" theory in light of competing evidence.

The jury similarly heard AstraZeneca's expert Dr. Jänne assert that "[t]here is no guidance in the Wyeth patent" for those "billions and billions of compounds" "about a unit dose for overcoming gefitinib[] resistant" NSCLC. Appx17490 (709:10-22). Again, the underlying billions assertion was not credible, and Wyeth's expert Dr. Hausheer explained to the jury that the patents teach the selection of a unit dosage calculated to achieve the desired therapeutic effect—i.e., "interfer[ing] with the EGFR pathway" thereby "kill[ing] cancer cells." Appx17519 (823:8-824:9). Dr. Hausheer explained why a unit dosage was adequately enabled and described, pointing to (for instance) the projected dosage range described in the specification, Appx17519 (824:14-825:19); Appx17520 (829:9-20) (noting experiments consistent with those projections), the patents' dosage comparisons to gefitinib, Appx17519 (825:7-19), information from irreversible inhibitors in other treatment settings, *e.g.*, Appx17519 (826:1-13) (noting that the listed irreversible inhibitors were "known" and "done before"), effective unit dosages already tested in animals, *e.g.*, Appx17520 (827:2-828:3), and the inventors' disclosure of concentrations of irreversible inhibitors that successfully inhibit EGFR, Appx17520 (828:4-829:5); *see also* Appx211 (15:54-59) (noting "the excellent correlation" between "clinical responsiveness" and laboratory cell lines with the relevant mutations). Thus, the jury heard and rejected AstraZeneca's claims that a unit dosage was not enabled or described.

E. JMOL

AstraZeneca raised 15 separate JMOL arguments on infringement, enablement, written description, anticipation, obviousness, and damages. Appx15077-79; Appx15663-65. AstraZeneca also moved for a new trial, Appx15700, and raised indefiniteness and equitable arguments in a subsequent bench trial, Appx15595. The court denied nearly all of AstraZeneca's post-trial arguments and rejected all of AstraZeneca's arguments tried to the bench. Appx27-69; Appx17133-68.

1. AstraZeneca Argued That Side Effects Preclude Identifying Doses Calculated to Produce a Therapeutic Effect

As to "unit dosage," AstraZeneca argued the claims were not enabled because post-priority evidence derived from a Phase I clinical trial of an irreversible EGFR inhibitor showed "tolerability issues" preventing irreversible inhibitors from "provid[ing] a desired therapeutic effect at a concentration that a patient can tolerate." Appx15088; *see also* Appx15688 (asserting that "clinical trials were necessary to determine the maximum tolerated dose," and that therapeutic doses for some compounds "could not be used" because they exceeded clinical-trial safety limits (emphasis omitted)). That Phase I clinical trial was not itself in evidence, and AstraZeneca never explained how the trial set its tolerability limit. *See* Appx17550 (949:12-950:3). AstraZeneca also raised a written description challenge to "unit

dosage" in a single, cursory paragraph that made no arguments distinct from enablement. Appx15695-96.

2. The Court Determined That a Unit Dosage Is Not Enabled or Described Due to the Court's Own Concerns About Lethal or Toxic Treatments

In considering enablement, the court reiterated its longstanding construction that "there is no requirement that the patents enable a 'unit dosage' that is acceptable in terms of lacking side effects, meeting the FDA's safety criteria, [or] having a particular level of effectiveness against a patient's cancer progression or other clinical symptoms." Appx57. Applying its longstanding construction of "unit dosage" to mean "'calculated to produce the desired therapeutic effect,'" Appx48, the court held that "AstraZeneca did not provide clear and convincing evidence that the claimed irreversible EGFR inhibitors do not achieve the desired therapeutic effect—inhibiting EGFR and killing cancer cells." Appx58 (quotation marks omitted).

However, the court proceeded to assess the trial record under a different, new construction. The court apparently found new meaning in the term "unit dosage," read in conjunction with "to the patient" (in the phrase "administering daily to the patient"), and held that the patents must also enable and describe a unit dosage within certain safety limits: "[I]f a POSA would have to undertake undue experimentation to find a 'unit dosage' that would not fatally poison a patient, then the patents-in-suit

do not enable a POSA to treat [gefitinib] resistant NSCLC in a patient by administering a daily unit dosage to a patient." Appx57-58. In other words, rather than the side effects and "tolerability issues," discussed at trial and in AstraZeneca's post-trial motions, *see* Appx15088—which the jury rejected as grounds for non-enablement—or even the notion, discussed by the court before trial, that it might be impossible to find a unit dose that could produce a therapeutic effect, *see* Appx17315-16 (12:22-13:8), the court rested its decision on concerns about "fatal[ity]," Appx57-58.

The court's analysis, however, cited no evidence that irreversible inhibitors were associated with fatality concerns. The court instead stated: "AstraZeneca presented unrebutted evidence that some dosages of compounds within the ranges specified by the patents-in-suit would be toxic to patients, and, more specifically, that the dosage level required for the compounds to be therapeutically effective could be unduly toxic to a patient." Appx59. The court failed to note that "toxicity" is a clinical term for side effects and does not equate to fatality risk. Nor did the court explain how its analysis could be squared with its unambiguous claim construction that "there is no requirement that the patents enable a 'unit dosage' that is acceptable in terms of lacking side effects." Appx57.

The court applied the same rationale in analyzing written description. Appx66-67. As with enablement, the court acknowledged that, under the claim

construction that governed trial, the jury could find that the patents contain "a sufficient written description of a process for disrupting EGFR pathways and eliminating cancer cells." Appx67. But it held the patents do not adequately describe the invention under the court's post-verdict reconstruction because, it said, the patents do not show the inventors were in possession of a safe, "administrable unit dosage—if any—for different compounds covered by the asserted claims." Appx67.

F. The District Court's Denial of Pre-Issuance Damages

Applying the jury's implied 3.5% royalty rate to sales during the pre-issuance period would result in a sizable award. But before trial, the court granted AstraZeneca's motion for summary judgment of no pre-issuance damages. The court held that because 35 U.S.C. § 154(d) does not expressly "incorporat[e] the language of section 271(b), which define[s] induced infringement," pre-issuance damages are unavailable for induced infringement. Appx104. Accordingly, Wyeth's pre-issuance damages claim was never decided on the evidence.

SUMMARY OF THE ARGUMENT

The district court never doubted that the patents enable a unit dosage that "achieve[s] the desired therapeutic effect—inhibiting EGFR and killing cancer cells"—and held that AstraZeneca "did not provide clear and convincing evidence" otherwise. Appx58 (quotation marks omitted). The court's written description

analysis likewise accepted that the jury could reasonably find "a sufficient written description of a process for disrupting EGFR pathways and eliminating cancer cells." Appx67. But when the court carried on and considered safety concerns under a new, post-verdict construction, it erred thrice over. Each of those errors independently requires setting aside JMOL.

First, the court's new construction was legally erroneous on its own terms. The court improperly imposed limitations that went beyond the claims and contradicted the established distinctions between standards for patentability and for clinical efficacy or FDA approval. The claims recite a unit dosage directed to the invention's "therapeutic effect"—inhibiting EGFR and killing cancer cells. The claims recite no safety or clinical efficacy requirements. Thus, whether the patents enable a *safe* unit dosage—particularly when measured against clinical-trial endpoints—is irrelevant and no basis for granting JMOL. *See, e.g.*, *United Therapeutics*, 74 F.4th at 1369 ("Absent incorporation of safety and efficacy requirements in the claims," arguments "concerning the safety and efficacy of treating … patients [are] not before us.").

Second, even accepting arguendo the court's post-verdict reconstruction, its JMOL decision fails on the evidence. The burden was *AstraZeneca's* to show that a jury could *only* conclude that it proved invalidity by clear and convincing evidence. *Mentor H/S, Inc. v. Med. Device All., Inc.*, 244 F.3d 1365, 1375 (Fed. Cir. 2001).

Cutting its own path, the court reasoned that the skilled artisan would have had to unduly experiment to identify which irreversible EGFR inhibitors "would not fatally poison a patient" when given as a "unit dosage." Appx57. (Its written description analysis rested on the same reasoning. Appx66-67.) But AstraZeneca advanced no "fatality" argument in its Rule 50 motions (or at trial). That is because no evidence showed that irreversible inhibitors carried significant lethality risk, much less to a degree that practicing the claims required undue experimentation or greater disclosure. Nor would a reasonable jury have been compelled to believe that skilled artisans would have needed to unduly experiment to determine which irreversible inhibitors could not be administered as a unit dosage for any reason—fatality risk or otherwise. Thus, to the extent the court relied on "unduly toxic" dosages as something less than lethal doses, that would not support JMOL either.

Third, even setting aside these two fatal flaws, the court's JMOL order procedurally erred in adopting a new, post-verdict construction that contradicted its prior construction—the construction determined at *Markman*, reiterated before and during trial, and on which the verdict was based. Again and again, the court was clear—the claims require no particular level of safety or satisfaction of any clinical endpoint. "[A]t the JMOL stage," it was beyond the court's power, and prejudiced Wyeth, to "adopt a new [or] more detailed interpretation of the claim language and

test the jury verdict by that new [or] more detailed interpretation." *Hewlett-Packard Co. v. Mustek Sys., Inc.*, 340 F.3d 1314, 1321 (Fed. Cir. 2003).

Each of these errors independently requires the grant of JMOL be set aside, the verdict reinstated, and the case remanded for further proceedings on Wyeth's post-trial claims for additional relief. (At minimum, these errors require a remand for further proceedings on enablement and written description.) And on remand, Wyeth should be allowed to pursue its claim for pre-issuance damages, which the court excluded based on an erroneous interpretation of 35 U.S.C. § 154(d).

STANDARD OF REVIEW

The district court granted JMOL to AstraZeneca based on enablement and written description, and it granted summary judgment to AstraZeneca on Wyeth's claim for pre-issuance damages. This Court reviews both orders *de novo*, applying the same underlying standards as did the district court. *Doby v. DeCrescenzo*, 171 F.3d 858, 873-74 (3d Cir. 1999) (JMOL); *DIRECTV Inc. v. Seijas*, 508 F.3d 123, 125 (3d Cir. 2007) (summary judgment).

JMOL—enablement and written description*:** A request for JMOL of invalidity layers two cumulative burdens on AstraZeneca. ***First, because patents are presumed valid, AstraZeneca was required to prove invalidity by clear and convincing evidence. *Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 95 (2011). Wyeth, by contrast, had "no burden to do anything to defend the validity of its patent

other than hold [AstraZeneca] to its own burden of persuasion." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (quotation marks omitted). ***Second***, once the jury rejected AstraZeneca's invalidity case, the JMOL standard raised the bar even higher: JMOL of invalidity is appropriate "only in extreme cases, when the [challenger] has established its case by evidence that the jury would not be at liberty to disbelieve and the only reasonable conclusion is in its favor." *Mentor H/S*, 244 F.3d at 1375; *see also Gay v. Petsock*, 917 F.2d 768, 771 (3d Cir. 1990) ("[S]uch action is reserved for those extreme circumstances where the effect of the evidence is not only sufficient to meet his burden of proof, but is overwhelming, leaving no room for the jury to draw significant inferences in favor of the other party."). In applying this framework, all evidence is viewed in the light most favorable to Wyeth, the verdict winner. *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351 (Fed. Cir. 2001); *Gay*, 917 F.2d at 771.

***Summary judgment—pre-issuance damages*:** The court's summary judgment of no pre-issuance damages rested solely on statutory interpretation, which is reviewed without deference. *DIRECTV*, 508 F.3d at 125.

ARGUMENT

I. THIS COURT SHOULD REINSTATE THE JURY'S VERDICT

The verdict should be reinstated for three independent reasons. ***First***, the claims require a unit dosage directed to the invention's desired therapeutic effect of

inhibiting EGFR and killing cancer cells; the district court erred by imposing additional lethality and toxicity limitations. ***Second***, even accepting those limitations, a reasonable jury was not required to find that AstraZeneca proved invalidity by clear and convincing evidence. ***Third***, the district court erred by granting JMOL based on a new construction adopted post-verdict. At minimum, these errors rendered the trial fundamentally unfair, requiring a remand for further proceedings.

Finally, because neither AstraZeneca nor the district court relied on any independent grounds for written description, those same errors require the court's written description holding to be set aside.

A. The Claims Must Enable a Unit Dosage Calculated to Produce the Desired Therapeutic Effect, Not a Dosage Free From Safety Concerns

An inventor must enable the skilled artisan to "make and use" the claimed invention. 35 U.S.C. § 112(a). In relevant part, Wyeth's patents claim "administering … a unit dosage of an irreversible [EGFR] inhibitor," Appx 221 (35:55-59), where a "unit dose" is "a predetermined quantity of active material calculated to produce the desired therapeutic effect," Appx208 (9:33-38); *see also* Appx2436-37 (claim construction order).

The key inquiry is thus whether the patents enable a unit dosage "that achieve[s] the desired therapeutic effect—inhibiting EGFR and killing cancer cells."

Appx58 (quotation marks omitted); Appx17519 (823:8-824:9). As the district court held, "AstraZeneca did not provide clear and convincing evidence" showing that aspect of a "unit dosage" was not enabled. Appx58. After all—as the patents disclose and Wyeth's expert Dr. Weiss explained—every irreversible inhibitor the inventors tested showed that it would inhibit EGFR and kill gefitinib-resistant cancer cells. *E.g.*, Appx17355 (169:19-170:8); Appx206 (5:58-6:3); Appx211 (15:54-16:28). And as Wyeth's expert Dr. Hausheer explained, the patents clearly teach a skilled artisan how to administer a dose that will inhibit EGFR and kill cancer cells. *E.g.*, Appx17519-20 (823:8-830:5) (noting relevant disclosures); *see also* Appx17548 (939:9-940:2) (explaining it would be "very standard" to select a unit dosage to "inhibit[] EGFR" based on "what is taught in the invention"). This is consistent with the patents' citations to contemporaneous literature where irreversible inhibitors showed benefit in other contexts using dosages taught by the patents. *E.g.*, Appx207 (7:25-36); Appx17519 (825:20-826:13) & Appx17520 (827:8-828:3) (Dr. Hausheer explaining why experiments in other contexts are helpful); Appx17876 (HKI-272 doses of 10-80 mg/kg/day "reduced tumor growth in a dose-dependent manner"); Appx17798 (level of "10 mg/kg/day" of EKB-569 inhibited tumor growth in cells overexpressing EGFR); Appx17519-20 (826:14-827:7). Even AstraZeneca's expert Dr. Taft admitted he could not identify a *single* irreversible inhibitor that had a therapeutic effect in the lab but not in patients.

Appx17492-93 (718:8-719:2). At bottom, there could be no doubt that the patents enable a unit dosage that will inhibit EGFR and kill cancer cells.

The district court, however, proceeded to hold that safety—specifically the absence of some undefined quantum of risk of lethality or excessive toxicity—was an element of the claims. The claims, according to the court's post-verdict construction, "must not only enable a unit dosage that produces the desired therapeutic effect," but also do so at levels that will not "fatally poison" or be "unduly toxic" to the patient. Appx57-59.

That construction was wrong. The claims' plain language and this Court's line of precedent including *United Therapeutics* foreclose the imposition of a safety requirement. The "actual words of the claim are the controlling focus," *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998), and "the language of the claim defines the scope," *Bell Commc'ns Rsch., Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 619 (Fed. Cir. 1995). The claims here say nothing about lethality, toxicity, or any safety endpoints set in clinical trials. Without any such claim language, these matters cannot be imported as limitations. *Cf.* A. SCALIA & B. GARNER, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 93 (2012) ("The principle that a matter not covered is not covered is so obvious that it seems absurd to recite it.").

The specification confirms that the inventors did not claim any particular level of safety. "When a patentee defines a claim term, the patentee's definition governs." *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 493 F.3d 1358, 1361 (Fed. Cir. 2007). Here, the inventors expressly defined "unit dose" with reference to "the desired therapeutic effect." Appx208 (9:33-38); *see* Appx2436-37. And the specification uses "therapeutic" in reference to agents "specifically targeted to the critical genetic lesions that direct tumor growth." Appx204 (1:49-51). The specification similarly explains that targeting EGFR is the inventors' "*therapeutic* intervention in the treatment of cancer." Appx204 (2:47-54) (emphasis added). The *whole problem* to which the invention is directed is "resistance" to gefitinib's "therapeutic effects"—not concerns about side effects. Appx205 (3:19-23).

The contemplated action of the irreversible inhibitors used in the claims—inhibiting EGFR (not reducing side effects)—bolsters that usage. The specification details what EGFR is, its three principal domains, and its activity, *see, e.g.*, Appx204 (1:53-63, 2:13-26, 2:47-64); Appx206-07 (6:63-7:9), and it teaches EGFR inhibitors' use for the specific purpose of "block[ing] a cell surface receptor responsible for triggering and/or maintaining the cell signaling pathway that induces tumor cell growth and division" and "interfer[ing] with the EGFR kinase domain." Appx204 (2:57-62); *see also* Appx211 (16:49-53) ("Inhibition of EGFR alone by an irreversible inhibitor … induce[s] apoptosis in gefitinib-resistant cells."). The

patents' figures likewise depict the results of irreversible EGFR inhibitors "in suppressing the T790M EGFR mutant." Appx206 (5:58-59); *see also* Appx206 (5:37-40) (showing "inhibition of EGFR … in cells treated with increasing concentrations of … the irreversible inhibitor"); Appx206 (5:60-63) ("comparison of gefitinib and two irreversible inhibitors … in their ability to suppress EGFR"); Appx206 (6:6-11) (showing "increased cell killing of NSCLC cells harboring an EGFR mutation"). By contrast, lethality and toxicity are never referenced in relation to a unit dosage or desired therapeutic effect.

AstraZeneca's argument for adding safety and clinical efficacy limitations to the term "unit dosage" relied on *other* terms used *elsewhere* in the specification—but *not* in the claims or in the definition of "unit dose": (1) the term "effective amount," which the specification defines as "an amount that results in a beneficial effect for at least a statistically significant fraction of patients," and (2) the term "effective" (and "effectiveness"), which the specification defines by way of "physiological safety" (i.e., "toxicity" and "side effects") and "pharmacological effectiveness" (i.e., "the ability of the treatment to result in a desired biological effect in the patient"). Appx207 (8:45-53); Appx210 (13:14-25); *see* Appx1128-29.

At claim construction, the district court correctly distinguished the different terms the inventors used. It observed that the inventors used "effective amount" (and "effective") elsewhere in the specification—not in the definition of "unit dose"

nor in the claims themselves. Appx2437. Instead, the claims use "unit dosage," and the specification defines "unit dose" as compositions containing "material calculated to produce the desired therapeutic effect." Appx208 (9:33-38).

At JMOL, however, the court appeared to newly rely on "unit dosage" read in combination with the recited administration "to the patient" to import a safety limitation found nowhere in its prior, consistent construction. *See* Appx57 ("The patents therefore must not only enable a unit dosage that produces the desired therapeutic effect, but also a unit dosage that can be *administered daily to the patient*." (original emphasis)). Not even AstraZeneca took this position. To the contrary, the parties *agreed* that the term "to the patient" "does not require construction" and takes its plain and ordinary meaning. Appx1958. That plain and ordinary meaning (i.e., human treatment subjects) specifies the claimed subject of administration, nothing more. *See Patient*, WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY ("WEBSTER'S") 1057 (1989) ("a person who is under medical or surgical treatment"); *see also, e.g.*, Appx204 (2:1); Appx205 (3:30, 3:37-39) (the invention is directed to treating "individuals" and "human cancers").

The claims are thus on all fours with this Court's decision in *United Therapeutics*. 74 F.4th 1360. There, the patentee claimed "a therapeutically effective … dose" administered "to a human." *Id*. at 1364. Like here, the accused infringer argued that the claims were not enabled and lacked written description

because they were insufficiently safe and effective in patients. *Id.*; *see* Opening Brief for Defendant-Appellant, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 22-2217, at 25, 28-31 (arguing that "the plain and ordinary meaning of 'treating pulmonary hypertension' … include[s] a method that accomplishes this goal both safely and effectively" and "requires safe and effective treatment that benefits patients … as opposed to killing them," and that "significant safety concerns" prevented enablement).

This Court rejected those arguments, because the claims "do not recite" safety or efficacy limitations, which the Court emphasized are "the FDA's responsibilities." *United Therapeutics*, 74 F.4th at 1369 (noting that the undisputed meaning of "therapeutically effective" was a dose "that causes an improvement in a patient's hemodynamics," and holding that such language "does not import any additional efficacy limitations or any safety limitations"). So too here: The therapeutic effect the claims contemplate is inhibiting EGFR and thereby killing cancer cells, which implies no safety limitations. "Absent incorporation of safety and efficacy requirements in the claims," arguments "concerning the safety and efficacy of treating … patients" miss the point because "[q]uestions of safety and efficacy in patent law have long fallen under the purview of the FDA." *Id.*

United Therapeutics follows a long line of precedent establishing that safety and clinical efficacy are the FDA's bailiwick and are typically unrelated to patentability:

> There is nothing in the patent statute … which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has stated are useful for "pharmaceutical applications," are safe, effective, and reliable for use with humans.

In re Krimmel, 292 F.2d 948, 954 (C.C.P.A. 1961). "Congress has given the responsibility to the FDA, not to the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use." *In re Anthony*, 414 F.2d 1383, 1395 (C.C.P.A. 1969); *see also, e.g.*, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the [FDA]. Title 35 does not demand that such human testing occur."). Nothing in the claims here displaces the default roles of the Patent Office and the FDA.

By demanding proof of human safety, the court contradicted this case law and effectively imposed a backdoor clinical testing prerequisite for method-of-treatment claims. *See* Appx60; Appx62-63; *see also* Appx15688 (AstraZeneca arguing that "clinical trials were necessary to determine the maximum tolerated dose"). That analysis would upend pharmaceutical claiming. Testing burdens "would prevent many companies from obtaining patent protection on promising … potential cures

in many crucial areas such as the treatment of cancer." *In re Brana*, 51 F.3d at 1568. While *regulatory* approval may require clinical testing, patent law does not. *See Scott*, 34 F.3d at 1063.

To be sure, inventors remain free to claim a treatment with particular safety or efficacy levels. *See, e.g.*, *Celgene Corp. v. Peter*, 931 F.3d 1342, 1347 (Fed. Cir. 2019) (claims reciting "a method for delivering a drug to a patient in need of the drug, *while avoiding the occurrence of an adverse side effect*" (emphasis added)). But the inventors here chose instead, as in *United Therapeutics*, to expressly define a unit dose to encompass only a therapeutic effect.

In sum, given the absence of safety and efficacy requirements in the claims, and given AstraZeneca's failure to prove lack of enablement (or written description) under the proper claim construction, *see* Appx58; Appx67, the grant of JMOL should be reversed and the jury's verdict reinstated.

B. Even Assuming the District Court's Post-Verdict Construction, the Jury's Verdict of No Invalidity Should Be Reinstated

Even if safety were a limitation, the JMOL grant could not stand. AstraZeneca never advanced a lethality argument, and a reasonable jury would not be compelled to accept such an argument, nor any argument of "undue toxicity."

1. AstraZeneca Never Advanced a "Lethality" Argument

The district court erroneously granted JMOL of invalidity based on a lethality theory of its own making. "It is for the *parties*—not the court—to chart the course

of the litigation." *Astellas Pharma, Inc. v. Sandoz Inc.*, 117 F.4th 1371, 1378 (Fed. Cir. 2024) (original emphasis). At JMOL, a court may determine only whether the defendant clearly and convincingly proved invalidity "by evidence that the jury would not be at liberty to disbelieve." *Mentor H/S*, 244 F.3d at 1375. A defendant cannot carry its invalidity burden under a theory it never advanced. *Astellas*, 117 F.4th at 1378.

AstraZeneca never argued that a skilled artisan would be precluded from practicing the full scope of the claims by a possibility of *fatal* unit dosages. In relevant part, its JMOL motions argued only that "tolerability issues" precluded calculation of a "unit dosage" because irreversible inhibitors "will not provide a desired therapeutic effect at a concentration that a patient can tolerate." Appx15088; Appx15688 (same). AstraZeneca never equated "tolerability" or "toxicity" with lethality. Indeed, its motions mentioned no possibility of death from administering irreversible inhibitors. In short, because AstraZeneca never asserted that skilled artisans "would have to undertake undue experimentation to find a 'unit dosage' that would not fatally poison a patient," Appx57, that was not a valid basis for granting JMOL.

2. A Reasonable Jury Could Easily Reject the Argument That Avoiding Lethality Would Require Undue Experimentation

Even if AstraZeneca had made a lethality argument, the trial evidence would not have supported it. Accordingly, no reasonable jury could find (much less be

compelled to find) clear and convincing evidence that determining "a 'unit dosage' that would not fatally poison a patient" would require undue experimentation. Appx57. Indeed, no witness from either side so testified. Besides, Wyeth is entitled to all reasonable inferences; AstraZeneca is entitled to none. *See McGinley*, 262 F.3d at 1351; *Gay*, 917 F.2d at 771. JMOL to AstraZeneca based on a lethality theory fails.

a. The Trial Record Does Not Compel Lack of Enablement for Supposed "Lethality" Concerns

Contrary to the district court's conclusion on lethality, the patents disclose prior art demonstrating the successful administration of irreversible inhibitors *without* lethal side effects. For example, Allen reports administration to breast-cancer patients of daily doses of CI-1033 (an irreversible inhibitor) that "ranged from 2 mg/d to 1,000 mg/d." Appx39617. Two-hundred-and-fifty cancer patients participated, Appx17459 (584:18-585:10)—none died. Instead, "adverse events [were] predominantly mild (grade 1) to moderate (grade 2) in intensity across a variety of doses." Appx39617. Severe side effects were "infrequent," and "no significant renal, hepatic, or cardiac toxicities" were observed. Appx39617. Even the more serious toxicities were "readily manageable." Appx39618.

Allen thus teaches, as AstraZeneca's expert Dr. Reider conceded, administration of daily dosages of an irreversible inhibitor to patients, and that "there's a dose described [in Allen] of 50 milligrams per day to 650 milligrams per

day." Appx17460 (589:18-24). The jury was entitled to note that Allen's administration of CI-1033 conformed with expectations: It did not kill patients, and its reported side effects were manageable. The jury was likewise entitled to credit Hidalgo's administration to patients of EKB-569 (an irreversible inhibitor the patents' specification expressly mentions), where "[t]he most frequently reported adverse events were diarrhea, rash, nausea, vomiting, stomatitis, and anorexia that were generally mild and reversible." Appx18499. And the jury could accept the evidence that (once more as expected) "EKB-569 was generally well tolerated, with an acceptable … safety profile, and offers a promising targeted approach to the treatment of solid tumors." Appx18499.

The district court also ignored Agus in this context, which teaches doctors to "overdose" nonresponsive patients—that is, to administer very high doses once or twice a week—using EGFR inhibitors in order to prompt a therapeutic effect. Appx17543 (921:23-922:25); Appx39579 (3:4-24). Specifically, Agus teaches the administration of any EGFR inhibitor (reversible or irreversible) "from about 500 mg to about 3,000 mg" once or twice per week, which "can be readily performed by one of skill in the art." Appx39583 (7:12-15, 7:26-27). AstraZeneca's expert Dr. Reider acknowledged that Agus "suggest[s] dosing" for irreversible inhibitors. Appx17461 (591:7-8). It was not unreasonable for a jury to note the overdoses of EGFR inhibitors in Agus and to conclude that daily doses (at much lower levels like

the ranges discussed in the patents) could likewise be administered to patients without killing them.

In fact, AstraZeneca's experts went so far as to rely on Allen and Agus to argue that they rendered the claims—including administration of a unit dosage—*obvious*. *E.g.*, Appx17459-61 (585:23-25, 589:7-590:5, 591:25-592:5) (Dr. Reider agreeing that a skilled artisan, combining Allen and Agus, would "understand that the two together provide specific dosing in patients and a recognition that irreversible EGFR inhibitors can be used and be administered to patients"); Appx17476 (651:19-25) (Dr. Jänne agreeing that multiple prior art references "disclose[] information about other irreversible EGFR inhibitors CI-1033, EKB-569, HKI-272 and their administration in the daily unit doses of 2 to 500 milligrams"); *see also* Appx150 (instructing the jury on Allen and Agus as prior art). Wyeth's witnesses explained why Allen and Agus taught away from the claims for other reasons. *See* Appx40-45 ("the jury was not required to find that a POSA would be motivated to combine Allen 2003 and Agus 2003"). But the jury was entitled to credit this evidence as showing that *calculating* dosages of irreversible inhibitors to *administer* to patients posed no obstacles. And as the inventor Dr. Haber explained, experiences from other settings remain instructive when it comes to patient dosing and side effects. Appx17397 (337:16-21) (emphasizing that "the drug actually is being used in patients in other settings"); Appx17398 (339:2-7) ("[W]hen you go to

patients, side effects don't matter whether you have lung cancer, breast cancer, or other cancers."). Finally, as Wyeth's expert Dr. Hausheer noted, selecting a unit dosage for these compounds to "inhibit[] EGFR" in light of "what is taught in the invention" would be "very standard" for the skilled artisan. Appx17548 (939:12-940:2) (explaining that Dr. Hausheer "do[es] this all the time" and that "[t]his is very standard").

The jury also heard evidence about clinical experience with gefitinib and animal studies using irreversible inhibitors, from which skilled artisans could draw in determining a non-lethal unit dosage. *E.g.*, Appx39617 (noting adverse events "predicted from pre-clinical animal experience, and … observed with other specific erbB receptor inhibitors"); Appx17483 (682:15-23); Appx17520 (827:2-7). For instance, the safety and efficacy of EKB-569, HKI-272, and CI-1033 were all modeled in mouse xenografts. Appx17798 (Greenberger; EKB-569); Appx17878 (Rabindran; HKI-272); Appx17845 (Wissner; EKB-569). These experiments all predicted "utility"—not lethality—for humans. Appx17798 (noting that EKB-569 inhibited growth of tumor cells overexpressing EGFR and concluding that "[t]hese data, combined with the safety assessment of EKB-569 in animals, suggest that EKB-569 may have utility in the clinic"); Appx17878 ("HKI-272 was well tolerated by the animals, and no weight loss or other compound-related toxicity was

observed."); Appx17845 ("On the basis of the work presented here … [EKB-569] is presently in [a] phase I clinical trial.").

Indeed, AstraZeneca's own witnesses' testimony stopped well short of suggesting lethality concerns. AstraZeneca's expert Dr. Jänne mentioned "skin rashes," "infections in the nail beds," and "gastrointestinal side effects" as side effects potentially caused by collateral inhibition of non-mutated (also called "wild-type") EGFR.[7] Appx17470 (630:2-11). AstraZeneca's expert Dr. Reider likewise posited only that "skin rash and GI toxicity" could "limit[] … maximal dosing." Appx17454 (563:25-564:5). And Dr. Ward, an AstraZeneca scientist who helped develop Tagrisso, similarly agreed that EGFR inhibitors' side effects "include diarrhea, skin rash, nail toxicity, and vomiting," with no mention of death. Appx17423 (440:16-22).

While the jury heard that these common side effects might "impact an individual's quality of life" and "are challenging to be dealing with," Appx17470 (629:17-630:14), such evidence does not amount to clear and convincing proof compelling a finding of fatality risk that would prevent administration of a unit dosage to a patient across the scope of the claims. To the extent that the record

[7] A reasonable jury did not have to treat Dr. Jänne's unexplained reference to "failure of organs like liver" as lethality. Appx17470 (630:2-11). AstraZeneca never attempted to equate liver failure with death. Nor could it, as liver failure can have lesser side effects akin to those discussed at trial (e.g., gastrointestinal issues).

contains *any* evidence of fatalities attributable to the side effects of irreversible inhibitors—once again, never discussed at trial—a jury was not required to conclude that such a risk precluded the skilled artisan from practicing the claims. Consider, for instance, the post-priority clinical trials supporting Tagrisso's use. In one trial, of 249 patients given Tagrisso, one patient experienced a fatal adverse reaction. Appx17760. But Tagrisso continues to be administered to patients in treatment settings every day. After all, "for any given method of treatment claim," there may be undesirable or adverse effects. *United Therapeutics*, 74 F.4th at 1371. That does not preclude administration, and the record contained no evidence that would require a jury to conclude a risk of fatality precludes practicing the claims.

b. The District Court's Lethality Reasoning Is Flawed and Not Supported by the (Minimal) Evidence It Cited

In reaching the opposite conclusion, the district court misunderstood key testimony. Specifically, the court conflated "toxic" dosages with "fatal" dosages. But as noted above, to a skilled artisan, "toxicity" is simply another term for side effects, or adverse events. *E.g.*, Appx210 (13:18-21) ("Physiological safety refers to the *level of toxicity*, or other adverse physiological effects at the cellular, organ and/or organism level (*often referred to as side effects*)." (emphases added)); Appx17423 (440:16-22) (discussing "toxicity" relating to "nail[s]," "skin rash" and gastrointestinal issues); Appx38900 (listing "toxicities" of grades 1-4 in a breast cancer clinical study, such as depression, diarrhea, and infection). And cancer

patients have long tolerated treatments with toxicities. Appx17386 (293:6-15) (chemotherapy is "quite toxic" but given to patients); Appx17758-60 (listing toxicities of gefitinib and Tagrisso).

The court's citations confirm that it improperly conflated toxicity with fatality. The court asserted that Wyeth's expert Dr. Hausheer agreed that "there is some level of toxicity—at the extreme, a fatal dose—that could not be administered to a patient." Appx57 (citing Appx17548 (939:24-940:5)). But the cited testimony comes nowhere near equating a *toxic* dose with a *fatal* dose. The surrounding discussion demonstrates the opposite: AstraZeneca was pursuing a line of questioning that equated a "toxic" dose with the clinical concept of a "maximum tolerated dose" (Appx17548 (940:6-8)), and a "maximum tolerated dose" can be calculated based on side effects like diarrhea and skin rash—not death, *see, e.g.*, Appx17454 (563:25-564:5) ("he's reporting that the skin rash and GI toxicity has limited their maximal dosing"). Dr. Hausheer's continued testimony confirmed there *was* activity regardless of AstraZeneca's "maximum tolerated dose": "a patient [can] get a therapeutic benefit that may not meet the standards for a particular clinical trial"—with no reference to fatality. Appx17550 (950:18-23).

In fact, all that Dr. Hausheer agreed to in that sequence was that practitioners "want to avoid administering a toxic dose in order to achieve the desired therapeutic effect." Appx17548 (940:3-5). It is unremarkable that clinicians prefer dosages that

avoid side effects. *Cf. Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 968 (Fed. Cir. 2023) ("varying a dose in response to the occurrence of side effects is well-known and obvious"); *United Therapeutics*, 74 F.4th at 1371 (noting that medical practitioners regularly assess which patients "should not take [a] claimed treatment"). It does not follow that the presence of side effects imposes undue experimentation—particularly given evidence showing the patents taught inhibiting EGFR and killing cancer cells in patients where other treatments failed. *See* Appx17353 (165:15-25); Appx17519 (823:22-824:5).

In equating testimony of toxicity with testimony of lethality, the court erred. The jury was not required to accept the conclusion that AstraZeneca had proven—by clear and convincing evidence—that irreversible inhibitors posed too great a risk of lethality to administer to patients simply because they could be "toxic" to varying degrees.

3. A Reasonable Jury Could Also Reject the Argument That Avoiding "Unduly Toxic" Dosages Would Require Undue Experimentation

To the extent the district court viewed an "unduly toxic" dose as something less than fatality, JMOL was also erroneous in light of the evidence.

Aside from references to fatality or lethality, the court never explained what it meant by an "unduly toxic" dose. The trial record is of little to no help; "unduly toxic" was never mentioned. Regardless, "unduly" signifies a comparison, meaning

"excessive[]" or "inappropriate, unjustifiable, or improper" in the circumstances. *Unduly*, WEBSTER'S 1547. A penalty, for instance, is "unduly harsh" when its severity is excessive. *E.g.*, *United States v. Inn Foods, Inc.*, 560 F.3d 1338, 1347 (Fed. Cir. 2009). To the extent the court did not mean death, it appears to have viewed an "unduly toxic" dosage as one that is excessively toxic.

A reasonable jury, however, was not required to find evidence (much less clear and convincing evidence) that practicing the claims while avoiding "undue toxicity" would require "undue experimentation." Patients with gefitinib resistance face a stark choice: allow their cancer to progress and die, or use irreversible inhibitors and risk potential side effects—even if severe. *See* Appx17387 (296:3-10); Appx206 (6:31-34). Given those options, a jury was not required to agree with the court that the side effects identified in the record were excessive.

Nor would a jury be required to accept AstraZeneca's theory that the skilled artisan could not calculate a unit dosage because some irreversible inhibitors might lack a therapeutic window—i.e., a dose calculated to produce a therapeutic effect might exceed a "maximum tolerated dose." Appx15088 (no "desired therapeutic effect at a concentration that a patient can *tolerate*" (emphasis altered)); Appx15688 (same). Setting aside that a "maximum tolerated dose" argument depends on a construction that erroneously includes safety and clinical efficacy requirements, *see supra* Part I.A, the evidence would not compel JMOL even under such a

construction. The court appeared to credit AstraZeneca's expert Dr. Jänne, who claimed the dosages taught by the patents might "not necessarily [be] unit doses because doses can be ineffective and not produce the desired therapeutic effect" or "be too toxic." Appx17475 (650:14-19); *see also* Appx17483 (681:3-8) (AstraZeneca's expert Dr. Taft asserting "if your toxicity threshold is here and you have to give a much higher dose in order to get activity … that means you will not achieve a therapeutic effect"). But that testimony was speculation a reasonable jury was entitled to reject.

First, Dr. Jänne's claim about the lack of a tolerable, therapeutic effect directly contradicts the mountain of inventor testing, clinical data, animal testing, and laboratory studies predicting and then showing just the opposite. *See supra* Part I.B.2; *see also* Appx206 (5:67-6:3) (inventors' testing shows "suppression of proliferation in … cells harboring … T790M mutations by the three irreversible [EGFR] inhibitors"); Appx17476 (651:19-25) (Dr. Jänne testifying that "[e]ach of Allen 2003, Greenberger 2000, Rabindran 2004, and Wissner 2002 discloses information about other irreversible EGFR inhibitors … and their administration in the daily unit doses of 2 to 500 milligrams." (as corrected, Appx15486)); *cf. Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309-10 (Fed. Cir. 2015) (even claims with "clinical profile limitations" adequately enabled even though "the specifications do not explicitly describe the clinical efficacy," because, based on data

and constructive examples in the specification, "the skilled artisan would not have questioned the utility … and would be able to make and use the claimed invention"). Again, AstraZeneca's expert Dr. Taft admitted he could not identify a *single* irreversible inhibitor that had a therapeutic effect in the lab but not in patients. Appx17492-93 (718:8-719:2).

Second, a reasonable jury could rely on evidence showing that the irreversible inhibitors used to practice the claims share features supporting their tolerability in patients. Wyeth's expert Dr. Jorgensen countered AstraZeneca's assertions that "billions" of irreversible inhibitors could be used to practice the claims; as Dr. Jorgensen explained, that was an "exaggeration" and "irrelevant." Appx17553 (962:9-16) ("A POSA wouldn't be thinking in those terms."). He also explained to the jury how these compounds' known features narrow the relevant universe for the skilled artisan. The chemical substituents that the skilled artisan would use to form covalent bonds, for instance, had the "right reactivity level" and would not "be too toxic." Appx17557 (976:2-4). Dr. Jorgensen also discussed "an extra benefit" of "known kinase inhibitor cores"—they "passed toxicity hurdles." Appx17557 (977:25-978:4); *see also* Appx17444 (525:6-526:7) (AstraZeneca's expert Dr. Reider acknowledging "examples of irreversible inhibitors that … showed benefit"). The district court's assessment entirely ignores this evidence that irreversible inhibitors were known in the prior art without concerns of undue toxicity.

Third, AstraZeneca did not present clear and convincing evidence that irreversible inhibitors actually required intolerable concentrations to achieve a therapeutic effect. AstraZeneca zeroed in on a single post-priority study, Godin-Heymann, which it argued showed that a single irreversible inhibitor, HKI-272, could not achieve a therapeutic effect in a patient below a posited maximum-tolerated serum concentration of 0.2μmol.[8] Appx39637. If it could demonstrate that HKI-272 was inoperative (again, according to a concocted toxicity standard), AstraZeneca seemed to believe that would mean other irreversible inhibitors could not be administered as a unit dosage without undue experimentation. Both the "inoperative" premise and the "undue experimentation" conclusion of this argument are mistaken.

To begin, the patents show that the tested irreversible inhibitors, *including HKI-272*, are, at every concentration tested, superior to gefitinib at disrupting EGFR and killing cancer cells in human cell lines containing T790M—even at 0.2μmol or below:

[8] A micromolar (μmol) represents an amount of substance per liter. One nanomolar (nm), used in the specification, equals 0.001μmol. For consistency, this brief converts evidentiary nanomolar values to micromolar values.

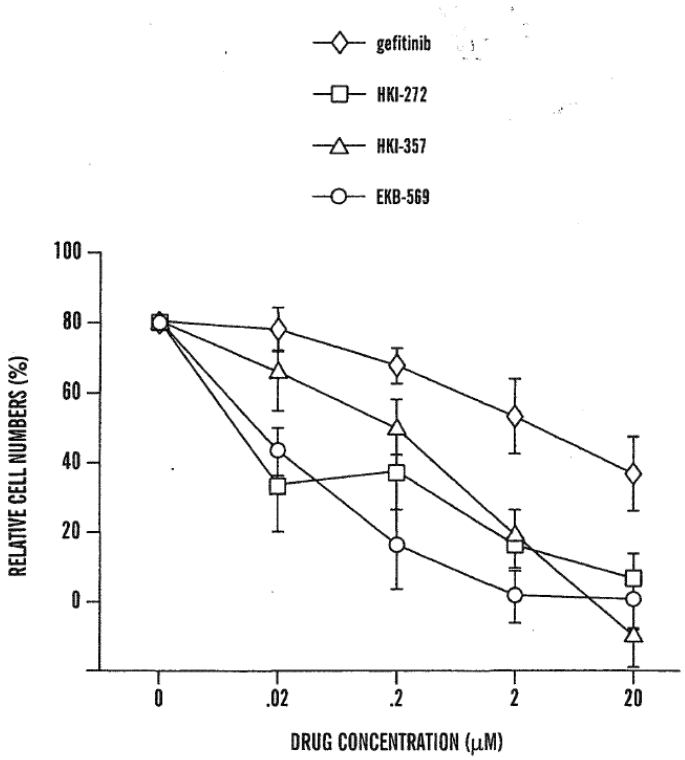

FIG. 4B

Appx198; *see* Appx206 (explaining that Figure 4B "shows suppression of proliferation in … cells harboring the [sensitizing] and T790M mutations by the three irreversible ERBB family inhibitors, compared with gefitinib"). Dr. Weiss discussed this data—as first published by the inventors in Kwak—to show that irreversible inhibitors "have a significant reduction in the number of cells that are still growing and dividing compared to gefitinib" across the concentrations tested in cell cultures with T790M. Appx17355 (169:19-170:8); Appx18201 (Fig. 4B). The jury was therefore not required to believe that HKI-272 (let alone other

embodiments) would not inhibit EGFR and kill cancer cells below AstraZeneca's 0.2μmol tolerability limit.

Wyeth's expert Dr. Hausheer also rebutted AstraZeneca's theory. Dr. Hausheer pointed the jury to the specification's disclosure of the EGFR-IC_{50} values—i.e., the concentration of active material required to inhibit 50% of EGFR activity in a cell—for HKI-272 and other compounds. Appx17520 (828:7-16); Appx211 (16:7-22). He testified that EGFR-IC_{50} values are "therapeutically important," and are used by skilled artisans to "optimize" dosing. Appx17520 (828:17-829:1). The specification discloses EGFR-IC_{50} values for HKI-272 and other irreversible inhibitors ranging from 0.034μmol to 0.092μmol—*below* AstraZeneca's asserted 0.2μmol limit. Appx17520 (828:7-16); Appx211 (16:7-22); *see also* Appx20297 (16:7-22) (Table 3); Appx17824 (Table 1). A reasonable jury was thus not required to find that surmounting AstraZeneca's (unproven) dosing obstacle for HKI-272 would require undue experimentation to practice the claims.[9]

Moreover, AstraZeneca's interpretation of Godin-Heymann is flawed. On its face, that study modeled potential mechanisms of resistance to *irreversible*

[9] Moreover, even if HKI-272 were inoperative, one such embodiment does not render the claims invalid or otherwise prove the skilled artisan would need to experiment unduly. *See Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid.").

inhibitors—not resistance to gefitinib—for the purpose of anticipating future resistance resulting from their use in patients. Appx39638 ("[P]revious experience with [tyrosine kinase inhibitors] indicates that tumor cells will eventually acquire resistance to even the most effective [inhibitors]. To anticipate molecular mechanisms that may underlie acquired resistance to irreversible [inhibitors], we modeled acquired resistance to … HKI-272."). The study reports that HKI-272 may not be able to completely "overcome" T790M-mediated resistance in cells bred specifically to resist HKI-272—based on a 0.2μmol tolerability limit established in a separate, Phase I *clinical* study. Appx39640. That HKI-272 may not "overcome" T790M-mediated *HKI-272 resistance* at that level, however, does not mean the jury was required to conclude that HKI-272 cannot provide a therapeutic effect against T790M-mediated *gefitinib resistance*. The patents are directed to the latter, not the former.

The district court emphasized testimony from Drs. Haber and Hausheer related to AstraZeneca's theory that irreversible inhibitors lack a therapeutic window. Appx60. Specifically, the court pointed to Dr. Haber's agreement that the patents studied concentrations "five times higher than the maximum tolerated dose for HKI-272." Appx17397 (336:14-337:9). But this quotation fails to note that Dr. Haber also pointed to evidence of irreversible inhibitors successfully administered to patients, Appx17397 (337:16-21) (disagreeing that the

concentrations "are too high to be administered," because "the drug actually is being used in other settings"), and that other concentrations reported in the patents showed utility within AstraZeneca's therapeutic window, Appx198; Appx211 (16:7-22). Similarly, the court quoted Dr. Hausheer's repetition of what Godin-Heymann claims, Appx17548 (943:1-944:1), but it failed to note that Dr. Hausheer's testimony pointed the jury to evidence showing that all inhibitors studied by the inventors would inhibit EGFR even within AstraZeneca's posited limits, Appx17520 (828:7-16); *see also* Appx198. The evidence thus does not support JMOL even accepting arguendo the court's new, post-verdict construction.[10]

C. The Post-Verdict Reconstruction Was Impermissible

Even if the court's post-verdict construction were substantively correct, and even if the evidence compelled a verdict for AstraZeneca on that construction, procedural considerations would still preclude JMOL for AstraZeneca. Specifically, the court erred when it added a new claim limitation after the verdict. "The verdict must be tested by the charge actually given," so "it is improper for the district court to adopt a new or more detailed claim construction in connection with the JMOL motion." *Hewlett-Packard*, 340 F.3d at 1320-21. Rather, the analysis "should have

[10] The court's case law discussion on "cull[ing] out inoperative embodiments" is likewise inapposite. Appx61-63. That discussion is based on its erroneous imposition of safety limits, and its flawed evidentiary assessment.

been limited to the question of whether substantial evidence supported the verdict under" the construction given to the jury. *Id.* at 1320.

Before trial, the parties agreed that, under the court's construction, the jury should be instructed that "unit dosage" bears the specification's express definition:

> physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluents; i.e. carrier, or vehicle.

Appx10660. Then, after AstraZeneca tried to introduce evidence on clinical efficacy, the court recognized that "basically part of the claim construction" is that clinical efficacy is not required, Appx17523 (840:13-842:16), and accordingly concluded its jury instruction on "unit dosage" with that point: "This claim term does not require clinical efficacy," Appx141-42; *see also* Appx2436-37, Appx13292-93 & Appx17315-16 (12:5-13:8) (prior rulings consistently holding that the claims do not include safety or efficacy limitations). The court never instructed the jury to interpret this meaning of "unit dosage" in light of the claims' reference "to the patient."

The court's post-verdict construction broke sharply from this approach. Despite its prior orders, the court reasoned that the patents "must not only enable a unit dosage that produces the desired therapeutic effect, but also a unit dosage that can be *administered daily to the patient*"—i.e., "a 'unit dosage' that would not fatally

poison a patient." Appx57 (original emphasis). The court similarly held that the patents must account for "unduly toxic" doses. Appx59. That was no mere "elabora[tion]" or "clarification" to "a construction that was inherent in the jury instructions and claim construction order." *Mformation Techs., Inc. v. Rsch. in Motion Ltd.*, 764 F.3d 1392, 1397-98 (Fed. Cir. 2014). It was a complete reversal from the court's ongoing adherence to its construction, including its emphasis at the start of the trial, that the claims did not require "this to be safe and efficacious or effective." Appx17315-16 (12:22-13:1). After the verdict, "it [was] too late" for such a change. *Hewlett-Packard*, 340 F.3d at 1321.

The district court thus made the same mistake this Court corrected in *Wi-Lan v. Apple*, 811 F.3d 455 (Fed. Cir. 2016). There, the district court instructed the jury using the claim construction that it had issued at *Markman* regarding the term "first computing means." *Id*. at 464-65; *see also id*. at 460 (reviewing the parties' claim construction arguments). That construction did not require a separate element known as a "complex multiplier." *Id*. at 464. In its jury instructions, the district court adhered to that view. *Id*. at 465. Nevertheless, the court's JMOL decision required a "complex multiplier" following repeated (but contested) testimony from Wi-Lan's witnesses—like AstraZeneca's witnesses here—that assumed such a requirement. *Id*. at 465-66. Based on its JMOL construction, the court reversed the jury on invalidity. *Id*.

This Court rejected that approach in no uncertain terms. It reiterated the rule that JMOL is "'too late … [to] adopt a new and more detailed interpretation of the claim language,'" and reinforced that, at JMOL, the trial court's analysis "is limited to whether substantial evidence supports the jury's verdict under the issued construction." *Id*. at 465 (quoting *Hewlett-Packard*, 340 F.3d at 1321). Because, as here, the district court added a new limitation relevant to invalidity after trial, the panel reversed. *Id*. at 466. And, as here, the court's error was "particularly conspicuous" because it added a limitation that was previously rejected. *Id*. at 465. Application of the same rule produces the same result here—reversal of the JMOL decision.

At minimum, the court's changed construction rendered the proceedings fundamentally unfair and warrants a remand for further proceedings. Because Wyeth had been repeatedly (and correctly) advised that the claims encompassed no safety requirements, it had no reason to develop additional safety evidence or present it at trial. *See Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1321 (Fed. Cir. 2009) ("Once a district court has construed the relevant claim terms, and unless altered by the district court, then that legal determination governs for purposes of trial."). When the court "construed the claims after trial, [it] changed the rules of the game." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1357 (Fed. Cir. 1998) (holding that a party, which accepted a late construction, was entitled to present new

evidence given that change). If the claims had been construed from the outset to encompass only "safe" or non-"toxic" dosages, Wyeth would have appropriately developed and presented additional evidence on these issues. *Cf.* Appx17559 (983:18-984:10) (striking testimony from Wyeth's Dr. Jorgenson explaining why AstraZeneca's "whole thing about dosing [is] a waste of time" as beyond the scope of his report). The court's about-face requires reversal, but, at the least, vacatur and remand.

D. AstraZeneca Is Not Entitled to JMOL on Written Description

A specification must "contain a written description of the invention." 35 U.S.C. § 112(a). "Whether a patent claim is supported by an adequate written description is a question of fact." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1297 (Fed. Cir. 2014). The district court's written description analysis tracked its enablement reasoning. Appx66-67. Likewise, AstraZeneca offered no written description argument independent from enablement. *See* Appx15695-96.

Because the court's written description holding mirrored its flawed enablement analysis, it too should be reversed for the reasons just described. Indeed, the court failed to credit the specification's disclosures as read by a skilled artisan. Appx17520 (828:7-16); Appx211 (16:7-22). The jury was not compelled to resolve this fact question in AstraZeneca's favor, let alone by clear and convincing evidence.

* * *

The district court's errors warrant reversal. At JMOL, it erroneously interpreted the claims, misread the trial evidence, and changed its construction too late. Each of those errors requires reversal of JMOL as to enablement and written description.

II. WYETH IS ENTITLED TO PURSUE PRE-ISSUANCE DAMAGES

At summary judgment, the district court interpreted 35 U.S.C. § 154(d) to "not authorize pre-issuance damages for induced infringement." Appx104. On that sole basis, it held that AstraZeneca "cannot be liable for pre-issuance damages." Appx105. This Court has not yet addressed whether § 154(d) provisional rights protect an inventor from *induced* infringement. This Court should reject the district court's interpretation and hold that § 154(d) provides just such protection.

Congress enacted § 154(d) in 1999. *See* American Inventors Protection Act of 1999, Pub. L. 106-113, § 4504, 113 Stat. 1501, 1501A-564. Before then, patent rights began only "on the date on which the patent issues." 35 U.S.C. § 154(a)(2). But in subsection (d), Congress added patent rights, called "provisional rights," that start "on the date of publication of the application for such patent … and end[] on the date the patent is issued." § 154(d)(1).

Under these provisional rights, "a patent shall include" the right to obtain a reasonable royalty, in limited circumstances, from anyone who, during that pre-

issuance period, "makes, uses, offers for sale, or sells in the United States the invention as claimed in the published patent application," § 154(d)(1)(A)(i), or, for process inventions, "uses, offers for sale, or sells in the United States … products made by that process as claimed in the published patent application," § 154(d)(1)(A)(ii). The limited circumstances described in subsection (d) require "the invention as claimed in the patent" to be "substantially identical to the invention as claimed in the published patent application," § 154(d)(2), that the defendant "had actual notice of the published patent application," § 154(d)(1)(B), and that the "action [be] brought not later than 6 years after the patent is issued," § 154(d)(3). Nothing in subsection (d) excludes induced infringement from its scope.

Contemporaneous sources make clear that subsection (d)'s provisional rights protect an invention claimed in a published patent application "as soon as your publication occurs" and "the same as though you had a patent"—including for induced infringement. 143 Cong. Rec. 5892 (Apr. 17, 1997) (statement of Rep. Hyde). For example, a Senate Report describes § 154(d) as directed to "infringement that occur[s] during the examination process" and entitling an applicant to "reasonable royalties from day one"—without caveat or limitation as to only certain types of infringement. S. Rep. No. 105-42, at 53 (1997); *see also id.* at 51 (provisional rights "enable [inventors] to collect a reasonable royalty for infringement that occurs during the time the application is published"); 143 Cong.

Rec. 5892 (Apr. 17, 1997) (statement of Rep. Hyde) ("[I]f anybody tries" to "tread on" the invention after its "publication occurs," "they are liable in damages for *infringement*" under provisional rights. (emphasis added)).[11]

The theory behind provisional rights is that "[p]ublication is protection"—in other words, publication "protects the inventor because he has provisional rights as against the world *as though he had a patent and can enforce it.*" 143 Cong. Rec. 6149, 6155 (Apr. 23, 1997) (statements of Rep. Hyde) (emphasis added); *see also id.* at 6141 ("you have provisional rights *as though you had a patent issued*" (emphasis added)); *id.* at 6155 ("If anybody wishes to infringe on your rights, which are called provisional rights, not a patent yet but *equivalent to a patent*, they are subject to damages. So you are protected." (emphasis added)). For § 154(d) to "protect[] the inventor … as against the world as though he had a patent," *id.* at 6149, it must offer protection against induced infringement.

The district court's contrary interpretation was incorrect. The court focused narrowly on specific words, rather than viewing the statute as a whole. The court's analysis turned on the fact that § 154(d)(1)(A)(i) and (ii) "parallel[] the language of

[11] The Senate Report and quoted floor statements addressed the addition of provisional rights by the proposed Omnibus Patent Act of 1997 and its counterpart in the House. The proposed pre-issuance patent rights would be enacted as part of the American Inventors Protection Act two years later in nearly identical form. *Compare* S. Rep. No. 105-42, at 21-23 *and* H. Rep. No. 105-30 (1997), at 15-26, *with* 35 U.S.C. § 154(d)(1)-(4).

35 U.S.C. §§ 271(a) and 271(g)" and do not expressly "incorporat[e] the language of section 271(b)." Appx104. To the court, "[t]he clear takeaway is that the statute does not authorize pre-issuance damages for induced infringement." Appx104.

The court misread that parallelism as excluding other types of infringement from provisional rights. The proper parallelism is between § 154(d) and its sister provision, § 154(a)—neither of which excludes induced infringement. Similar to the language in § 154(d)(1)(A)(i) and (ii), § 154(a) states that "[e]very patent" shall include "a grant to the patentee … of the right to exclude others from making, using, offering for sale, or selling the invention … and, if the invention is a process, of the right to exclude others from using, offering for sale or selling … products made by that process." § 154(a)(1). Just like § 154(a)'s patent rights plainly encompass protection against induced infringement, not solely infringement under § 271(a) and (g), so too for § 154(d). Section 154(d) had no need to expressly "incorporat[e] the language of section 271(b)," Appx104, any more than § 154(a) did.

Moreover, the court's analysis was flawed because it disregarded the broader statutory language and context. Section 154(d) was enacted not only in light of the preexisting provisions in § 154 (including § 154(a)) but also in light of § 271. Under § 271(a), "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States … during the term of the patent therefor, infringes the patent." And under § 271(b), "[w]hoever actively induces infringement

of a patent shall be liable as an infringer." Those provisions must be read alongside § 154(d)'s grant of provisional rights for a patent. When read "as a whole"—as statutes must be, *e.g.*, *Gustafson v. Alloyd Co.*, 513 U.S. 561, 570 (1995)—and in light of § 154(d)'s clear congressional purpose, those who actively induce others to practice an invention claimed in a published patent application are every bit as "liable as an infringer," § 271(b), as those who "make[], use[], offer[] to sell, or sell[]" the invention, § 271(a); *accord* § 154(d)(1)(A)(i).[12]

The court also incorrectly tried to distinguish § 271(b) from § 154(d) based on § 271(b)'s reference to "a patent." In the court's view, § 271(b) differs from § 154(b) because it "covers induced infringement 'of a *patent*'" whereas "pre-issuance damages occur before any patent exists." Appx105 (emphasis by the court). But there is no such distinction. By its own terms, § 154(d)'s provisional rights are rights of "a *patent*." § 154(d)(1) (emphasis added). Accordingly, there is no inconsistency between § 271(b)'s reference to "a patent" and allowing for pre-issuance inducement damages under § 154(d).

Finally, the court observed that § 154(d) is a "narrow exception" to the rule that damages are generally available only for conduct during the patent term.

[12] The court's statement that "Wyeth does not dispute that AstraZeneca's alleged conduct falls outside the scope" of § 154(d) again looked at the specific words rather than the context as a whole. Appx104.

Appx103; Appx105. But Wyeth's reading properly leaves § 154(d)'s scope narrow. As discussed above, provisional rights apply only if a panoply of requirements are met, such as having "actual notice of the published patent application." § 154(d)(1)(B), (2)-(3); *see also* S. Rep. No. 105-42, at 53 (1997) (emphasizing these statutory limitations—without suggestion of limiting provisional rights based on type of infringement). Accordingly, Wyeth's reading maintains § 154(d) as "a 'narrow exception' that permits recovery only for certain conduct that is specifically enumerated in the statute." Appx105.

By contrast, the court's interpretation improperly attributes illogic to Congress. Under the court's reading, doctors infringing Wyeth's claims would be liable for pre-issuance damages, but pharmaceutical companies like AstraZeneca that actively encourage and induce such infringement would not. Nothing requires this Court to endorse such a result. *See, e.g.*, *Jones v. Hedrix*, 599 U.S. 465, 479 (2023) ("We generally resist attributing to Congress an intention to render a statute so internally inconsistent." (quotation marks omitted)); *Dupuch-Carron v. Sec'y of Health & Hum. Servs.*, 969 F.3d 1318, 1330 (Fed. Cir. 2020) (collecting citations for the proposition that "if a literal construction of the words of a statute be absurd, the act must be so construed as to avoid the absurdity" (cleaned up)).

The proper interpretation of § 154(d) permits pre-issuance damages for induced infringement. The Court should therefore remand the case for further

proceedings on Wyeth's pre-issuance damages claim—a claim that, given Tagrisso's substantial sales during the period between publication of the applications for the patents and the patents' issuance, is not insignificant.

CONCLUSION

AstraZeneca has not met its JMOL burden. The verdict should be reinstated, and the case should be remanded for further proceedings on Wyeth's requests for pre-issuance damages and other relief. At minimum, the case should be remanded for further proceedings on enablement, written description, and pre-issuance damages.

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Respectfully submitted,

/s/ *Jennifer L. Swize*
Jennifer L. Swize
JONES DAY
51 Louisiana Avenue, N.W.
Washington, DC 20001
(202) 879-3939

Anthony M. Insogna
Meredith A. Stewart
Daniele San Román
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, California
(858) 314-1130

Jason G. Winchester
JONES DAY
110 North Wacker Drive, Suite 4800
Chicago, IL 60606
(312) 269-4373

Gasper J. LaRosa
JONES DAY
250 Vesey Street
New York, New York
(212) 326-7885

Matthew J. Rubenstein
JONES DAY
90 South Seventh St., Suite 4950
Minneapolis MN, 55402
(612) 217-8800

Daniel Paul Johnson
JONES DAY
500 Grant Street, Suite 4500
Pittsburgh, PA 15217
(412) 394-7217

Counsel for Appellant Wyeth LLC