No. 2024-2325

United States Court of Appeals for the Federal Circuit

WYETH LLC,

Plaintiff-Appellant,

v.

ASTRAZENECA PHARMACEUTICALS LP AND ASTRAZENECA AB,

Defendants-Appellees.

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

RESPONSE BRIEF OF DEFENDANTS-APPELLEES ASTRAZENECA PHARMACEUTICALS LP AND ASTRAZENECA AB

Christopher N. Sipes
Einar Stole
Megan P. Keane
R. Jason Fowler
COVINGTON & BURLING LLP
850 Tenth Street NW
Washington, DC 20001
(202) 662-6000

Counsel for Defendants-Appellees

CLAIMS AT ISSUE

The claims at issue are claims 1, 3, and 9 of U.S. Patent No. 10,603,314 and claim 1 of U.S. Patent No. 10,596,162. Claim 1 of the '314 patent and claim 1 of the '162 patent are illustrative of the issues in the appeal and are reproduced here:

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.

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.

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 AstraZeneca Pharmaceuticals LP and AstraZeneca AB

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.
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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: 03/13/2025

Signature: /s/ Christopher N. Sipes

Name: /s/ Christopher N. Sipes

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
AstraZeneca Pharmaceuticals LP		AstraZeneca PLC
AstraZeneca AB		AstraZeneca PLC

☐ 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

Kaveh Saba Covington & Burling LLP	Eric R. Sonnenschein Covington & Burling LLP	Priscilla Dodson Covington & Burling LLP
Ashley Winkler Covington & Burling LLP	Melissa Keech Covington & Burling LLP	Tobias Ma Covington & Burling LLP
Elaine Nguyen Covington & Burling LLP	Robert T. McMullen Covington & Burling LLP	Jason Reinecke Formerly with Covington & Burling LLP

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

(continued)

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

Karen E. Keller Shaw Keller LLP	Andrew E. Russell Shaw Keller LLP	Nathan R. Hoeschen Shaw Keller LLP
Emily S. DiBenedetto Shaw Keller LLP	Jeff Castellano Formerly with Shaw Keller LLP	

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TABLE OF ABBREVIATIONS

’314 patent	U.S. Patent No. 10,603,314, issued March 31, 2020
’162 patent	U.S. Patent No. 10,596,162, issued March 24, 2020
Wyeth’s patents or patents-in-suit	collectively, ’314 and ’162 patents
asserted claims	collectively, claims 1, 3, and 9 of the ’314 patent, and claim 1 of the ’162 patent
Tagrisso	The accused product, Tagrisso® (osimertinib)
Court	U.S. Court of Appeals for the Federal Circuit
district court	U.S. District Court for the District of Delaware, Judge Matthew F. Kennelly (by designation)
EGFR	epidermal growth factor receptor
NSCLC	non-small cell lung cancer
gefitinib-resistant NSCLC	gefitinib and/or erlotinib resistant non-small cell lung cancer
POSA	person of skill in the art
FDA	U.S. Food and Drug Administration
USPTO	U.S. Patent and Trademark Office
JMOL	judgment as a matter of law
AstraZeneca	collectively, Defendant-Appellees AstraZeneca Pharmaceuticals LP and AstraZeneca AB
Wyeth	Plaintiff-Appellants Wyeth LLC
Godin-Heymann publication	Godin-Heymann et al., *The T790M “Gatekeeper” Mutation in EGFR Mediates Resistance to Low Concentrations of an Irreversible EGFR Inhibitor*, MOLECULAR CANCER THERAPEUTICS (Vol. 7 No. 4) 874-9 (2008)
Kobayashi publication	Kobayashi et al., *EGFR Mutation and Resistance of Non-Small-Cell Lung Cancer to Gefitinib*, NEW ENGLAND JOURNAL OF MEDICINE (Vol. 352 No. 8) 786-92 (2005)
’008 patent	U.S. Patent No. 6,002,008
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)
Cross	Cross et al., *AZD9291, an Irreversible EGFR TKI, Overcomes T790M-Mediated Resistance to EGFR*

	Inhibitors in Lung Cancer, CANCER DISCOVERY (Vol. 4 No. 9) 1046-61 (2014)
Cheng	Cheng et al., *Recent Progress on Third Generation Covalent EGFR Inhibitors*, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (Vol. 26 No. 6) 1861-8 (2016)

STATEMENT OF RELATED CASES

No appeal from the district court in this action has previously come before this or any other appellate court. In addition, AstraZeneca is not aware of any case pending in this or any court or agency pursuant to Rule 47.5 that will or could be directly affected by the Court's decision in this case.

INTRODUCTION

Wyeth's patents purport to claim methods of treating patients with a particular type of non-small cell lung cancer ("NSCLC"). But it was AstraZeneca, not Wyeth, that discovered the key to treating these patients. For its part, Wyeth filed an incomplete patent application that taught the wrong solution, and the inventors later learned that the laboratory data disclosed in their specification did not translate into treating patients. Rejecting the teachings of Wyeth's patent applications, AstraZeneca developed Tagrisso®—a drug that remains the only treatment option specifically for the resistant patients Wyeth's patents purport to treat. Tagrisso had been FDA-approved and administered to cancer patients for nearly five years before Wyeth—who had long-abandoned any development efforts—was finally issued broad, functionally defined method claims drafted to capture far more than the inventors actually discovered or described. After hearing the trial testimony, the district court correctly held that Wyeth's asserted claims are invalid for lacking enabling or written-description support as a matter of law. The court's judgment should be affirmed.

In particular, Wyeth's patents claim methods of treating patients with gefitinib-resistant NSCLC by administering an irreversible epidermal growth factor receptor ("EGFR") inhibitor in a "unit dosage." Both the administered inhibitor and dosage are defined functionally. The irreversible EGFR inhibitors encompass any

compound that binds to, and irreversibly inhibits, the EGFR protein, and the "unit dosage" requires a "predetermined amount…calculated to produce the desired therapeutic effect." But when the Wyeth applicants filed their applications in 2005, they had conducted only *in vitro* laboratory studies on three compounds. Subsequent attempts to treat patients failed. The inventors had targeted the wrong form of EGFR, one also found in healthy cells, leading to dose-limiting toxicity that prevented administration ***to patients*** of high enough doses to kill resistant cancer cells. Wyeth's *in vitro* studies, conducted in the lab on isolated cancer cells, are blind to this problem, as the lead inventor Dr. Haber acknowledged: "[t]he concentrations in the test tube are higher than those you can give to patients." Appx17397-98 (337:10-15, 339:8-11). The drug concentrations in the patents were ***five times higher*** than what could be administered to patients. Appx17397 (336:22-337:8).

The district court correctly held that Wyeth's patents failed to enable or adequately describe the claimed methods of treating. The claims require that a clinician "calculate[]" the amount of an irreversible EGFR inhibitor that will "produce the desired therapeutic effect" "in a patient." But the specification describes no unit dosage for any irreversible EGFR inhibitor, nor a method for calculating such a dosage for the full scope of irreversible EGFR inhibitors claimed. Appx17397 (336:22-337:3); Appx17549 (943:1-13). The specification contains no working examples, describing only *in vitro* experiments. Prediction of clinical

dosing from *in vitro* studies is "extremely challenging." Appx17396 (334:6-8) (Haber); *see also* Appx15150 (131:1-4), and the *in vitro* drug concentrations in the patents cannot be achieved in patients, as they far exceed toxicity limits. The district court correctly concluded "the specification describes an unfinished project, not a completed invention." Appx67.

Moreover, the claims are remarkably broad and encompass a vast genus of inhibitors defined solely by function, yet the specification identifies only three compounds (that are structurally and functionally similar) for practicing the claimed methods and provides no working examples even for those. The district court's judgment should be affirmed.

STATEMENT OF THE ISSUES

1. Did the district court correctly hold that the patents-in-suit do not enable or provide written-description support under 35 U.S.C. § 112 for the full scope of the administered daily "unit dosage" of the asserted claims?

2. In the alternative, should the district court's judgment of invalidity be affirmed because the patents-in-suit do not enable or provide written-description support under 35 U.S.C. § 112 for the full scope of the irreversible EGFR inhibitors of the asserted claims?

3. Did the district court correctly hold that, even if valid and infringed, Wyeth is not entitled to damages under 35 U.S.C. § 154(d) for conduct that occurred before the patents-in-suit issued?

COUNTER-STATEMENT OF THE CASE

A. Wyeth Did Not Solve the Problem of Treating Gefitinib-Resistant NSCLC

1. EGFR Inhibitors and Gefitinib-Resistant NSCLC

When the patent applications were filed in 2005, the EGFR inhibitors gefitinib and erlotinib were FDA approved for the treatment of NSCLC—the most common form of lung cancer. Appx204 (1:45-46, 2:41-64); Appx17467 (616:4-10). EGFR is a naturally occurring protein in humans that is necessary for cell growth; abnormally high levels of it had been observed in some NSCLC patients. Appx204 (1:64-2:12, 2:27-40); Appx17442 (518:3-10). To treat NSCLC, researchers therefore designed

gefitinib and erlotinib to bond with the EGFR protein and inhibit (or stop) its activity. Appx204-205 (2:65-3:18); Appx17470 (628:7-22).

Gefitinib and erlotinib were just the "first generation" of EGFR inhibitors tested in patients. *See* Appx204-205 (2:65-3:10); Appx17469 (625:5-9). They were designed to inhibit "wild-type" EGFR (i.e., the naturally occurring form of the protein present in both healthy cells and most NSCLC cells). Appx17470 (628:12-629:2). The chemical bonds that first generation inhibitors form with EGFR are "reversible" meaning that they can break under the physiological conditions in a human body. Appx17469 (625:5-9).

By 2005, researchers were already developing the "second generation" of EGFR inhibitors. Like first-generation inhibitors, these second-generation inhibitors were designed to bond to wild-type EGFR, but were developed to be more potent by forming "irreversible" bonds with EGFR that will not break under physiological conditions. Appx17480 (667:11-14); Appx17453 (561:16-562:4).

By that time, it was clear that the NSCLC in some patients was resistant to gefitinib (i.e., did not respond). Appx205 (3:19-23). First, in 2004, several different researchers discovered that gefitinib treatment was associated with response (the tumors shrank) when the NSCLC harbored certain "sensitizing" mutations in EGFR, while NSCLC with naturally occurring "wild-type" EGFR appeared resistant (the tumors continued to grow despite treatment). Appx17471 (633:4-22); Appx17815-

17816; Appx41470. Then, in February 2005, two different research groups reported an additional mutation called T790M[1] that was present in patients who initially responded (the tumors initially shrank) but eventually became resistant to gefitinib (the tumors resumed growing). Appx39643-39644; Appx17861.

In addition to disclosing the T790M resistance mutation in gefitinib-resistant NSCLC,[2] researchers at the Dana Farber Cancer Institute also reported (in their Kobayashi publication) *in vitro* experiments demonstrating that an irreversible EGFR inhibitor appeared effective against gefitinib-resistant NSCLC with T790M. Appx39643, Appx39647-39648; *see also* Appx17458 (579:4-580:5). Prior-art publications such as Allen and Agus had previously proposed treating resistant NSCLC with an irreversible EGFR inhibitor. Appx39615-39617; Appx39582-39583.

2. Wyeth Rushed to Patent the Use of Irreversible EGFR Inhibitors Before They Had Developed a Completed Method

Prior to learning of the Kobayashi publication, Dr. Haber and his team were testing irreversible inhibitors *in vitro* using other types of resistant cell lines and had just filed a patent application that did not describe testing of gefitinib-resistant

[1] The mutation is T790M because it reflects the replacement of a Threonine with a Methionine at EGFR's 790th amino acid.

[2] "Gefitinib and/or erlotinib resistant NSCLC" is referred to herein as "gefitinib-resistant NSCLC." *See* Br.7, n.3.

NSCLC with T790M.[3] After learning about the Kobayashi publication, Dr. Haber felt "scooped," and rushed to perform an "urgent project" to test cells with T790M (as in Kobayashi). Appx41029; Appx17393 (321:1-322:17). In April 2005, they filed a second patent application to include T790M. Appx17393 (322:14-17); Appx17458 (580:6-581:13).

Dr. Haber's applications described only *in vitro* experiments studying the activity of three structurally related, second-generation EGFR inhibitors: HKI-272, HKI-357, and EKB-569. Appx207 (7:26-36); Appx17396 (333:25-334:5); *see also* Appx15230; Appx17441 (511:2-512:20). All three—like all second-generation inhibitors—preferentially bind to wild-type EGFR. Appx17480 (667:11-14); Appx17453 (561:16-562:4); Appx15141 (180:18-181:06). Wyeth's specification teaches that the target of the claimed irreversible inhibitors is "cysteine 773 of EGFR (SEQ ID NO: 1)," Appx205 (3:57-59), which designates wild-type EGFR, Appx15129 (117:22-24).

The specification does not describe the administration of these or any other irreversible EGFR inhibitor to any patient. Appx17484 (683:11-684:14); Appx17472 (637:16-25, 638:14-16). Nor did it disclose either the unit dosage for these or any other irreversible EGFR inhibitor to be administered to treat gefitinib-

[3] The first application reported that resistance to gefitinib was ***not*** due to an additional (i.e., secondary) mutation like T790M. Appx17620-17621 (¶66); Appx17395 (329:12-16).

resistant NSCLC or how to calculate such a dosage. Appx17455 (568:25-569:16); Appx17470 (627:15-628:2); Appx17563 (1000:18-24). Although the specification describes the range of potential doses as "from about 1 to 1000 mg" and "preferably from about 2 to 500 mg," Appx207 (8:59-66), these ranges captured virtually all possible doses and do not enable a POSA to identify the administrable dose for any particular compound to practice the claimed methods. Appx17490-17491 (709:25-711:9).

3. Wyeth Later Learned that Its Inhibitors Could Not Be Administered to Patients in Doses to Inhibit Gefitinib-Resistant NSCLC

After the patent applications were filed, Wyeth attempted to use the inhibitors identified in the applications to treat patients with gefitinib-resistant NSCLC. A fundamental problem emerged: the *in vitro* concentrations reported in the applications could not be achieved in patients because they far exceeded toxic limits. As Dr. Haber acknowledged, when they filed their applications, they did not know what amount of the tested irreversible EGFR inhibitors could be administered to patients. Appx17397 (336:1-21). The subsequent clinical testing revealed that "the ***concentrations*** that [they] were studying and reporting in [their] patent were ***five times higher than the maximum dose***." Appx17397 (336:22-337:9) (emphases added). In Dr. Haber's words, "[t]he concentrations in the test tube are higher than those you can give to patients." Appx17398 (339:8-11).

The inventors explain in their 2008 Godin-Heymann publication that the "concentrations required *in vitro* may not be achievable in patients due to drug toxicity." Appx11804, Appx11807; *see also* Appx17548 (942:3-13). They do not identify any dose of their inhibitors that can be used in patients to inhibit EGFR T790M. Instead, they conclude there is "clearly a need" to develop new inhibitors to overcome gefitinib resistance but do not describe what those inhibitors should look like. Appx11807; Appx15130 (145:2-16); *see also* Appx39669, Appx39678; Appx39651, Appx39656.

4. AstraZeneca Developed a New Type of EGFR Inhibitor to Treat Gefitinib-Resistant NSCLC in Patients

AstraZeneca solved the problem Wyeth could not by designing a new, third-generation EGFR inhibitor—Tagrisso. Appx17413 (400:2-15); Appx17416 (411:13-412:2). To develop Tagrisso, AstraZeneca rejected the guidance in the field, including the work by Wyeth and the inventors, which taught the use of an inhibitor that targets wild-type EGFR. Appx17412-17413 (395:21-396:21, 401:20-402:9); Appx17477 (658:1-16). Instead, AstraZeneca developed ***Tagrisso*** so that it ***preferentially bonds with mutant EGFR while sparing wild-type EGFR*** (that is, Tagrisso inhibits mutant EGFR with much greater potency than wild-type). Appx17411-17414 (392:22-393:3, 395:21-404:3); Appx17470 (629:13-630:18).

AstraZeneca designed and evaluated thousands of compounds with a new structure in pursuit of a mutant-selective EGFR inhibitor, eventually arriving at

Tagrisso. Appx17414 (404:4-406:24); Appx17418-17419 (419:1-423:18). Tagrisso demonstrated, in doses that can be administered to patients, the ability to inhibit T790M-mutant EGFR with reduced inhibition of wild-type. Appx17467 (618:21-24); Appx174670 (627:7-14); Appx15133 (179:17-20). FDA approved Tagrisso for the treatment of NSCLC patients with T790M in 2015, and today—nearly a decade later—Tagrisso remains the only FDA-approved treatment shown to specifically benefit those patients. Appx17697; Appx17468-17469 (622:21-623:6); *see also* Appx17480 (667:18-668:3).[4]

Dr. Haber and his team did not invent any wild-type sparing, mutant-selective irreversible EGFR inhibitor, Appx17396 (333:5-7); Appx17479 (663:4-14), much less Tagrisso, Appx17396 (332:23-333:4). Indeed, as Dr. Haber conceded, when he learned of the mutant-targeted approach in 2010, five years after he filed his patent applications, he recognized it as a "new development" that for the first time could provide a drug capable of treating gefitinib-resistant NSCLC in patients. Appx15131-15132 (172:4-12, 178:6-19); Appx39624-39625.

Given Tagrisso's success, as part of the patents' prosecution, Wyeth submitted Tagrisso's approved Product Label and two publications about Tagrisso ("Cross" and "Cheng"), purportedly as evidence of the unexpected benefits arising

[4] Since before 2020, the majority of Tagrisso's patients are treated for other FDA-approved indications for NSCLC without T790M and only certain "sensitizing" mutations. Appx17469-17470 (624:3-19, 627:7-14); Appx17479 (664:24-665:3).

from Wyeth's claimed methods of treating. *See* Appx37112-37114. The USPTO rejected Wyeth's argument because Tagrisso is ***not*** representative of the inhibitors described in Wyeth's applications:

> Cross teach[es] that Tagrisso/AZD9291 is structurally and pharmacologically distinct from other tyrosine kinase/EGFR inhibitors…. Cheng teaches that while the second generation EGFR covalent inhibitors potentially inhibit wild-type EGFR and cause toxicities, the third generation of EGFR TKIs like Tagrisso/AZD9291 have high potency against the T790M mutant EGFR and selectivity over wild-type EGFR. Thus, ***the activity of the Tagrisso***/AZD9291 appears ***not to be representative*** of the broadly claimed irreversible EGFR inhibitors.

Appx37311 (citations omitted, emphasis added).

5. Wyeth Pursued Broad Claims by Distinguishing the Prior Art Based on Alleged Effectiveness and Tolerability

The Wyeth applicants spent a decade at the USPTO claiming to have invented broad methods of treating such patients by administering an irreversible EGFR inhibitor. The examiner cited prior art describing the use of irreversible EGFR inhibitors in resistant NSCLC, and Wyeth struggled to distinguish its claims. In response, Wyeth repeatedly emphasized the "highly unpredictable nature of the art," and told the USPTO they had developed an "effective" method for treating gefitinib-resistant cancer. Appx38540-38541 (distinguishing Kobayashi's *in vitro* research as failing to teach an "effective" method of treating); Appx36977 (distinguishing Agus's teaching to administer an irreversible EGFR inhibitor to overcome gefitinib

resistance because the art was "highly unpredictable," and the inhibitor was known to be "not effective").

Wyeth subsequently amended the claims to add the requirement of a daily "unit dosage" to distinguish prior art (Agus) that it said taught "overdosing" of an irreversible inhibitor. Appx37074, Appx37076-37077; Appx38609. Wyeth contrasted the claimed "unit dosage" from Agus' "overdoses" that Wyeth argued were "not well-tolerated" and unsuitable for daily administration. Appx37415; *accord* Appx39327-39330.

In March 2020—five years after FDA approved Tagrisso—the patents-in-suit issued.

B. The District Court's JMOL of Invalidity

In September 2021, Wyeth sued AstraZeneca, alleging inducement based on Tagrisso sales. Throughout the district court proceedings, AstraZeneca maintained that the Wyeth patents are invalid, among other reasons, for failing to comply with §112.

1. Claim Construction

The asserted claims broadly recite methods of treating gefitinib-resistant NSCLC "in a patient" by daily administering any of a genus of "irreversible EGFR inhibitors" in a "unit dosage." Appx221; Appx269. The '162 patent claims a dosage range of 2-500 mg, while the '314 patent has no

limitation. At Markman, the district court adopted the following constructions, which applied throughout the proceedings below:

Preamble. The district court held that the preambles are statements of intended purpose that are limiting and have their plain and ordinary meaning. Appx2421-2427.

Unit dosage. The district court adopted the specification's definition of "unit dose": "a predetermined quantity of active materials calculated to produce the desired therapeutic effect." Appx2435 (quoting Appx208 (9:34-38)). Wyeth asserted that "the specification does not define therapeutic effect," and argued that no additional construction was needed. Appx1130. The district court agreed with Wyeth over AstraZeneca's objection, concluding that "[no] construction beyond the definition as stated in the specification" was required. Appx2437.

Irreversible EGFR inhibitor. The district court held that the genus of inhibitors is functionally defined and construed the genus to encompass any agent that (1) irreversibly inhibits EGFR, and (2) covalently binds to a particular location on EGFR, Appx2431, except that the '162 patent excludes a single inhibitor (CL-387,785). Appx2430-2435. The district court rejected Wyeth's argument that the claimed genus was limited to specific structural classes, stating "this focus on what the irreversible inhibitors do—rather than what they are—leads the Court to

conclude that a functional definition of the term stays true to the claim language and most naturally aligns with the patent's description." Appx2433-2434 (cleaned up).

2. The Evidence at Trial

The evidence at trial established that a POSA would not have been able to make and use the full scope of the claimed genus of irreversible EGFR inhibitors, in part because a POSA would not have been able to administer the claimed inhibitors in a "unit dosage" "in a patient." Even if the desired therapeutic effect is inhibiting EGFR and killing cancer cells, the record demonstrated that irreversible EGFR inhibitors encompassed by the claims cannot be administered to a patient in an amount that is calculated to produce this effect.

It was undisputed that a toxic dose is not a "unit dosage." Wyeth's invalidity expert Dr. Hausheer admitted that "in order to achieve the desired therapeutic effect," the POSA will "want to avoid administering a toxic dose." Appx17548 (940:3-5); *see also* Appx17548 (939:24-940:2, 940:6-8). Inventor Dr. Rabindran admitted that "[t]he maximum tolerated dose is the highest dose that can be used therapeutically in patients." Appx15145 (110:20-24); *see also* Appx17396 (334:20-23).

It was further undisputed that a POSA could not administer certain claimed irreversible EGFR inhibitors, including the preferred embodiments, in a "unit dosage." Dr. Haber admitted that at the time the inventors filed their applications,

they did not know how much HKI-272 could be administered to a patient. Appx17397 (336:1-8). Experts from both parties and Dr. Haber agreed that following the patent applications, the inventors discovered the amount of HKI-272 required to inhibit cancerous EGFR with T790M is five times more than the maximum amount that can be administered to a patient—that, it is not possible to administer enough HKI-272 to inhibit and kills cancer cells with EGFR T790M. Appx17397 (336:21-337:15); Appx17548 (942:2-20); Appx17489-17490 (706:14-708:18). Thus, the record established that there is no unit dosage of HKI-272 that can be administered to a patient and inhibit EGFR in cancer cells harboring T790M. Appx17490 (707:22-708:18); Appx17479 (666:7-18); *see also* Appx17549 (943:2-15); Appx17483 (681:3-10). As to the two remaining disclosed embodiments, Wyeth's expert admitted that the maximum tolerated dose of EKB-569 "is even lower" than HKI-272, and today, we still do not know the maximum tolerated dose of the final described compound, HKI-357. Appx17549 (943:2-944:1); *see also* Appx17563 (1000:18-24).

Unrebutted evidence at trial confirmed that nothing in the specification would have guided a POSA to a "unit dosage" administrable to a patient for the full scope of claimed irreversible EGFR inhibitors. Appx17484 (683:6-20, 684:7-14); Appx17490 (709:17-22); Appx17491 (711:15-713:17); Appx17470 (627:23-628:6); Appx17472-17473 (637:10-639:2). The specification does not identify the unit

dosage for even a single inhibitor. Appx17491 (712:5-6, 713:2-4); Appx17563 (1001:11-21). Inventor Dr. Sordella admitted that a POSA could not calculate a unit dosage, even for the three tested compounds, based on the *in vitro* experiments in the specification. Appx15149-15150 (129:7-131:11). And, beyond the three preferred embodiments—the specification does not provide guidance to determine which of the many possible irreversible inhibitors would satisfy the claims and at what dose. Appx60-61.

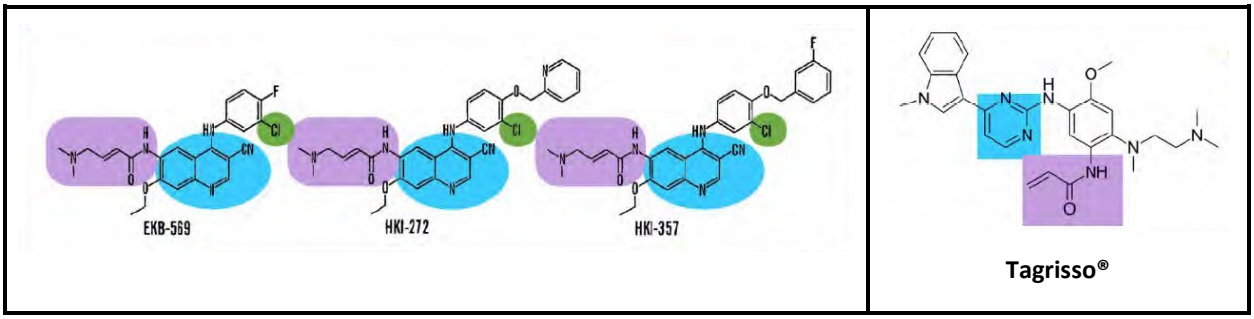
The evidence at trial demonstrated that each compound must be separately tested to determine whether it has activity against gefitinib-resistant EGFR ***in a patient***. Even if a compound has *in vitro* activity, it may not be administrable in a unit dosage for many reasons—e.g., the compound may not be able to be formulated into a drug product, may not be able to permeate cell walls, and/or may bind to the wrong target in the patient's body. Appx17482-17483 (678:5-680:12, 681:18-682:6); Appx17562-17563 (997:6-998:13); Appx15149-15150 (129:7-131:4). But a POSA could not determine this until the compound is tested through extensive preclinical and eventually clinical testing. Appx17481-17483 (674:8-678:4, 682:7-14); Appx17563 (1001:11-21, 1002:2-22); Appx17456 (570:20-571:2). Accordingly, the record evidence showed that the amount of experimentation required to determine whether a compound could be administered in a unit dosage

(and in what amount), would have been significant. *E.g.*, Appx17491 (711:15-713:17); Appx17455-17456 (568:10-21, 571:3-13).

Moreover, the evidence at trial established that identifying a unit dosage for the full scope of the claimed genus of irreversible EGFR inhibitors would not be possible. Although the parties disputed the precise number, there was no dispute that the genus of irreversible EGFR inhibitors encompassed by the asserted claims is vast, comprising a diverse range of structures. Appx17447 (535:8-20, 537:9-18); Appx17560-17563 (990:17-991:1, 991:20-992:2, 992:8-11). Yet a POSA would have to test each one to determine whether it could be used to practice the claimed methods of treating.

The evidence at trial established that the specification fails to disclose species that are representative of the vast claimed genus. Dr. Reider demonstrated that the scope of the claimed inhibitors is significantly broader than the three structurally related species identified in the specification. For example, as shown below, the accused Tagrisso compound has a significantly different structure than each of the structurally related species disclosed. Appx17441 (512:21-513:13); *see also* Appx17452-17453 (558:16-20, 559:3-13, 562:10-23); Appx15140 (176:9-14). HKI-272, HKI-357, and EKB-569 share the same structural core (blue: two-ring 3-cyanoquinoline), same active warhead (purple: dimethylaminobutenamide), and

same chlorine substituent (green: "Cl"). Tagrisso, by contrast, has a different core (single-ring pyrimidine), different active warhead (acrylamide), and has no chlorine.



Appx15231.

In addition, despite Wyeth's assertion that the asserted claims cover the mutant-selective Tagrisso compound, the inventors admitted at trial that the specification does not describe any wild-type sparing, mutant-selective inhibitor. Appx17396 (333:1-7); *see also* Appx17560 (990:4-8). To the extent Dr. Jorgensen testified that a POSA would focus on particular structures, he notably did not opine that the three disclosed species are representative of the claimed genus, nor did he point to any other disclosure in the specification identifying allegedly useful structures. The trial record thus left no doubt that the full scope of the claimed genus of irreversible EGFR inhibitors was not described in the specification.

Despite the trial evidence, the jury returned a verdict finding the claims valid and infringed. Appx163-174.

3. JMOL

Following trial, AstraZeneca filed a motion seeking, *inter alia*, JMOL of invalidity because no reasonable jury could have concluded that Wyeth's specification enables or adequately describes the full scope of the claimed "unit dosage" or genus of irreversible EGFR inhibitors. The district court granted JMOL because the claims lack both adequate enabling disclosure and written description to support the claimed "unit dosage."

Claim construction. The district court reaffirmed its claim constructions and prior orders, confirming that they applied in its JMOL decision: "the asserted claims therefore require neither FDA approval nor clinical effectiveness." Appx56. Instead, "the claims require only that the 'unit dosage' 'produce[s] the desired therapeutic effect' in a patient." *Id*.

Enablement. The district court rejected Wyeth's contention that "the patents are enabled as long as the method of treatment interferes with the EGFR pathway and kills cancer cells." Appx57. Rather, the patents claim "a method for treating [gefitinib-resistant NSCLC] *in a patient*… comprising administering daily *to the patient*… a unit dosage." *Id*. The court concluded "that AstraZeneca presented clear and convincing evidence such that no reasonable jury could find that the patents-in-suit enabled a POSA to administer a unit dosage of any irreversible EGFR inhibitor covered by the claims *to a patient* without undue experimentation." Appx58. "Wyeth

did not provide any evidence to rebut AstraZeneca's evidence that some dosages of irreversible EGFR inhibitors that fall within the claims could be toxic if administered to patients." Appx60.

The district court cited the Supreme Court's recent decision in *Amgen v. Sanofi*, 598 U.S. 594 (2023), noting that "the patent must provide some guidance that will reliably enable a [POSA] to make and use ***all of what is claimed, not merely a subset***." Appx61 (internal quotations omitted, emphasis added). Following the guidance in *Amgen*, the court explained that "the patents-in-suit do not teach which unit dosages of compounds covered by the claims could be administered daily to a patient and which could not. Thus, the patents-in-suit provide only a starting point, a direction for future research." Appx62 (internal quotations omitted). The court accordingly held the claims invalid for lack of enablement.

Written description. The district court independently held the claims invalid for lacking written description, explaining that a POSA would be required to engage in significant experimentation to determine an administrable unit dosage—if any—for different compounds covered by the claims. Appx66-67. "With respect to a method of treatment involving administering daily a unit dosage to a patient, the specification describes an unfinished project, not a completed invention." Appx67.

Irreversible EGFR inhibitor. As to the claimed genus of irreversible EGFR inhibitors, the district court denied AstraZeneca's JMOL motion. The court

determined that the conclusory trial testimony of Wyeth's expert Dr. Jorgensen, which asserted that a POSA would have been able to make a "handful" of the vast genus of irreversible EGFR inhibitors, was a sufficient basis for the jury's verdict. Appx51-52; Appx65-66; *see also* Appx17558-17559 (982:16-983:4).

C. The District Court's Denial of Wyeth's Request for Pre-Issuance Damages Under § 154(d)

Wyeth accused AstraZeneca only of induced infringement, Appx5271 (¶27); Appx7460 (¶27), and sought monetary damages, which included a request for pre-issuance damages under §154(d). Appx7461 (¶29); *see also* Appx8912-8915. AstraZeneca denied that it infringed and moved for summary judgment, in relevant part, of no pre-issuance damages. Appx5242-5265. The district court granted AstraZeneca's motion in part, agreeing that §154(d) does not authorize pre-issuance damages for inducement. Appx103-105. The court did not reach AstraZeneca's second argument that Wyeth's pending claims are not a "publication" as required by the statute.

SUMMARY OF THE ARGUMENT

The district court's judgment of invalidity should be affirmed. Wyeth's claims go far beyond what is enabled and described in the specification. Wyeth's specification discloses three structurally similar compounds purporting to show anti-cancer activity in *in vitro* gefitinib-resistant cell lines. But that is not what Wyeth claims.

The mismatch between the specification and the claims runs afoul of the enablement and written-description requirements. As the district court recognized, Wyeth's patents' claim the treatment of gefitinib-resistant NSCLC "in a patient" "by administering daily to the patient…a unit dosage." Appx57. Yet Wyeth's specification provides no examples of administering a "unit dosage" to a patient. Nor does the specification describe what the "unit dosage" is for any of the three embodiments. And importantly, Wyeth's claims are not limited to those three structurally similar embodiments. Instead, Wyeth purports to claim administration of a unit dosage of each of a broad functional class of irreversible EGFR inhibitors that bind at a particular location in EGFR. As the court explained, "the patents-in-suit provide only a starting point, a direction for future research," Appx62, and "an unfinished project, not a completed invention," Appx67. The district court's judgment should be affirmed for at least each of the following reasons.

First, the district court correctly concluded that "AstraZeneca presented clear and convincing evidence such that no reasonable jury could find that the patents-in-suit enabled a POSA to administer a unit dosage of any irreversible EGFR inhibitor covered by the claims *to a patient* without undue experimentation." Appx58. Each of Wyeth's arguments to the contrary fails. The district court applied the claim construction that ***Wyeth*** advocated. AstraZeneca provided unrebutted evidence that

under Wyeth's construction, the claims are not enabled. Wyeth cannot now argue that it has been prejudiced when it seeks a claim construction never requested below.

Second, the district court correctly concluded that the "patents-in-suit do not contain a written description that clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed, i.e. a unit dosage of an irreversible EGFR inhibitor that can be administered daily to [a] patient." Appx66 (cleaned up). Wyeth's brief does not substantively address the court's determination and, for that reason alone, the court's decision should be affirmed. But in any event, the trial record is clear that a POSA would not understand the inventors to have been in possession of the claimed unit dosage for the full scope of inhibitors claimed. Indeed, the inventors admitted at trial that they were not in possession of the claimed "unit dosage."

Third, the district court's judgment may be affirmed on the alternative ground that the specification fails to enable or adequately describe the full scope of claimed irreversible EGFR inhibitors, which are claimed functionally as any compound that irreversibly inhibits EGFR by binding to a designated residue. But the specification provides no guidance to a POSA regarding how to determine the full scope of compounds that can be used in the claimed methods—identifying only three structurally similar compounds (that cannot be administered in the claimed unit dosage) and providing no guidance about common structural features for the

functionally claimed compounds. A POSA following the specification would be faced with unguided trial-and-error to identify a relevant compound, which is insufficient as a matter of law.

Moreover, the specification fails to show possession of the broad class of compounds claimed. The specification discloses only a few structurally similar inhibitors but never describes species representative of the inhibitors that Wyeth now seeks to claim, such as Tagrisso. Tagrisso is structurally and functionally different from what is described in the specification, and the inventors admitted that they did not invent mutant-selective inhibitors like Tagrisso.

Because the judgment of the district court should be affirmed, this Court need not reach Wyeth's arguments on pre-issuance damages, but if it does, the district court's judgment that Wyeth is not entitled to pre-issuance damages should be affirmed.

STANDARD OF REVIEW

JMOL is appropriate "where a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have had a legally sufficient evidentiary basis to find for the party on that issue." *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1142 (Fed. Cir. 2019); *see* Fed. R. Civ. P. 50(a).

ARGUMENT

I. The District Court Correctly Held the Claims are Invalid Because the Specification Does Not Enable their Full Scope

The enablement requirement of 35 U.S.C. § 112(a) ensures that, "upon the expiration of the patent, the knowledge of the invention inures to the people, who are thus enabled without restriction to practice it." *Amgen*, 598 U.S. at 605 (cleaned up). "[T]he more a party claims for itself the more it must enable." *Id.* at 616. An inventor may attempt to claim an entire class of an alleged invention, but if so "the patent's specification must enable a person skilled in the art to make and use the entire class" without unreasonable experimentation. *Id.* at 610; *accord Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1367 (Fed. Cir. 2023).

The claims Wyeth asserts here are broad. They encompass administering an irreversible EGFR inhibitor in a functionally-defined daily "unit dosage"—an amount calculated to produce the desired therapeutic effect "in a patient." The specification discloses only three structurally similar inhibitors for carrying out the claimed method and discloses no unit dosage even for those three. It is undisputed that the specification contains no working example of the claimed methods nor any *in vivo* studies of gefitinib-resistant NSCLC. The specification reports solely *in vitro* studies of resistant cell lines in petri dishes that the inventors here admitted do not provide a means of determining a unit dosage.

In holding the claims not enabled as a matter of law, the district court accepted Wyeth's position that the "desired therapeutic effect" was inhibiting EGFR and killing cancer cells but recognized that the claims required achievement of this therapeutic effect "in the patient." Appx56-57. As the court held, this imposes a toxicity limitation, since, as Wyeth's own expert acknowledged, to achieve the desired effect in patients, the unit dosage of the claims could not be unduly toxic. Appx57 (quoting Appx17548 (939:24–940:5)). But Wyeth's specification provides no teaching to a POSA to find any unit dosage. Instead, the specification suggests preferred dosing ranges that encompass toxic doses even for the three identified inhibitors, and "provide no guidance that would help a POSA reliably screen between compounds that would have the desired therapeutic effects at toxic versus non-toxic dosage ranges." Appx59-60; Appx62-63. In the court's words, the patents provide "only a starting point, a direction for future research," which is insufficient as a matter of law to meet the enablement requirement. Appx62 (quoting *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 939-41 (Fed Cir. 2010)).

Wyeth attacks the district court's judgment on three grounds, arguing that it erred by (1) applying the claims to require the administered "unit dosage" to be below toxic limits; (2) determining the trial record established that the patents failed to enable a POSA to determine such a unit dosage for the full class of irreversible inhibitors claimed; and (3) purportedly changing the meaning of the claim post-

verdict. Br.27-28. These arguments lack merit. Both the trial record and the intrinsic evidence confirm the court correctly held the claimed daily dosage requires avoidance of dose-limiting toxicity and that the trial record establishes that Wyeth's patents fail to enable such dosing. Wyeth's assertion that the court sprang that requirement upon it post-trial is contradicted by the procedural history of the case. At Markman, ***Wyeth*** asked the court ***not*** to further construe the "desired therapeutic effect" or provide further guidance about its meaning. And the court denied Wyeth's pretrial motion to exclude evidence of the dose-limiting toxicity because it is relevant to enablement and written description. *See* Appx17315-17316 (11:6-21, 12:18-13:21).

A. The District Court Correctly Applied the Claims to Require Avoidance of a Toxic Dose

Wyeth first argues that the district court erred by requiring the administered "unit dosage" not to be unduly toxic. Br.28-36.

Any ambiguity in the meaning of "unit dosage" was entirely Wyeth's doing. The district court construed the term "unit dosage" to mean, as Wyeth requested, "a predetermined amount … calculated to produce the desired therapeutic effect." Appx2436 (quoting Appx208 (9:34-38)). Wyeth argued that term required no further construction, and the court agreed. Appx1130; Appx2437. Wyeth has therefore forfeited any opportunity to seek further construction. *See, e.g.*, *In re Google Tech.*, 980 F.3d 858, 863 (Fed. Cir. 2020).

In any event, Wyeth is incorrect that the district court imposed specific safety or efficacy requirements. On the contrary, as it did throughout the proceeding, the court reiterated its determination that the specification need not enable a "unit dosage" with particular safety or efficacy requirements. For example, in its decision the court stated "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***, having ***a particular level of effectiveness*** against a patient's cancer progression or other clinical symptoms, or meeting any other criteria that might make a drug an attractive option for a practicing clinician." Appx57 (emphases added). The court continued that "the fact that an extensive amount of experimentation may be necessary to find an ***ideal or optimal dose is not relevant*** to the enablement inquiry." *Id*. (emphasis added).

But that did not mean that there was no limit on the claimed "unit dosage" at all. Instead, as the district court observed, the claim language required the administered unit dosage be "calculated to produce the desired therapeutic effect" "*in a patient*." Appx56-57. The ordinary meaning of this requirement is that the dosage cannot be unduly toxic to the patient—particularly because the claim requires the dosage to be administered daily to the patient. Appx57. Wyeth points to no record evidence to the contrary.

The trial record confirms that the claimed methods could not be carried out with toxic doses. Wyeth's own expert conceded that "unit dosage" required avoidance of toxic dosing:

> Q. When you calculate a unit dose, do you make sure that dose is not so high it's going to be toxic to the patient?
>
> A. Yeah, you have several unit doses that you're going to use. This is very standard.
>
> Q. And so you'll want to avoid administering a toxic dose in order to achieve the desired therapeutic effect, correct?
>
> A. Yeah.

Appx57 (quoting Appx17548 (939:24-940:5)). Wyeth mischaracterizes this testimony by asserting its expert was talking about clinicians' "preference" to avoid side effects. *See* Br.44-45. Its expert's plain words contradict Wyeth, as he specifically testified as to what was required to "calculate a unit dose" and "achieve the desired therapeutic effect." Appx17548 (939:24-940:5).[5] The district court heard the testimony and understood what Wyeth's expert conceded.

The intrinsic evidence also makes clear that the claimed "unit dosage" requires avoidance of toxic dosing. During prosecution, Wyeth added the requirement of a "unit dosage" to distinguish prior art that disclosed treating resistant NSCLC by administering a "resistance-surmounting quantity" of an irreversible

[5] Wyeth admits "unit dosage" and "unit dose" are interchangeable. Br.15, n.6.

EGFR inhibitor. Appx37074. Wyeth disparaged the "resistance-surmounting" dosing of the prior art as "overdosing" and argued the prior art's teaching of "administering an overdose" would lead a POSA away from the claimed "unit dosage," which Wyeth emphasized required an amount "calculated to produce the desired therapeutic effect." Appx37076-37077. Wyeth then further amended the claims to require daily administration of the unit dosage, arguing that the prior art taught away, "because increased daily dosages [resistant-surmounting quantity] ***are not well-tolerated***." Appx37415 (emphasis added); *see also* Appx37413 (distinguishing "the daily administration of a specified unit dosage" of the pending claims from the "'resistance-surmounting quantity' (*i.e.*, an overdose)" of the prior art); *accord* Appx39328-39330. Having itself distinguished the daily "unit dosage" of the claims from the "overdose" of the prior art on the basis of tolerability, Wyeth cannot now complain that the district court likewise understood its claimed methods of treating as excluding excessively high dosing that cannot be tolerated by patients on daily administration.

Wyeth erroneously argues that the district court's decision is contrary to *United Therapeutics Corp. v. Liquidia Technologies*, 74 F.4th 1360 (Fed. Cir. 2023). *See* Br.33-34. That case involved a claim requirement of a "therapeutically effective single dose," which the court construed "to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics." *United*

Therapeutics, 74 F.4th at 1369. There, the record evidence showed that the claimed method (administration of a single dose of the drug treprostinil) did improve patients' hemodynamics, rendering the claim enabled. *Id.* at 1370. And, contrary to Wyeth's argument, in *United Therapeutics*, this Court did not hold toxicity irrelevant to any method-of-treating claim. Rather, it affirmed that, there, safety concerns did not prevent a POSA from carrying out the claimed method. *See id*.

Both the claims and the trial record in this case are therefore distinguishable from *United Therapeutics*. First, unlike the single dose required there, here the Wyeth patents claim daily administration of a unit dosage calculated to produce the desired therapeutic effect, which the intrinsic evidence and trial testimony confirm requires a POSA to avoid toxic dosing. Second, unlike the trial record in *United Therapeutics*, where the single claimed drug could be administered in the claimed "single event dose" to patients to achieve the claimed therapeutic effect, here the trial record refutes that the full range of claimed irreversible EGFR inhibitors can be administered in a daily dosage to achieve the desired therapeutic effect in patients (even if that effect is inhibiting EGFR and killing cancer cells). As the district court observed, the trial record established that there are many inhibitors for which no dose may be found, and Wyeth's patents provide no guidance for selecting those which may be used. Appx59-63. Nor does the specification provide working examples or

describe a unit dosage for any inhibitor. Appx58-59. The case here is thus completely different from that in *United Therapeutics*.

Moreover, Wyeth mischaracterizes *United Therapeutics* as "holding that such language ["therapeutically effective"] 'does not import any additional efficacy limitations or any safety limitations.'" Br.34. To the contrary, this Court held the meaning of "therapeutically effective single event dose" was not before it as not appealed. *United Therapeutics*, 74 F.4th at 1369.[6] This Court thus did not have occasion to address the meaning of "therapeutically effective," let alone address the meaning of a dose "calculated to produce the desired therapeutic effect" in the context of daily administration, the claim requirement at issue here.

B. The District Court Correctly Held the Specification Fails to Enable a POSA to Practice the Full Scope of the Claimed Invention

Wyeth next incorrectly argues that the district court's JMOL conclusion is not supported by the evidence.

As an initial matter, Wyeth is wrong that "AstraZeneca never advanced a 'lethality' argument." Br.36-37. AstraZeneca consistently maintained that a POSA could not practice the claimed invention because dose-limiting toxicity precluded

[6] Moreover, in quoting *United Therapeutics*, Wyeth elides over the claim requirement of a "single event dose," Br.33, and never addresses the district court's recognition that, here, the "unit dosage" must be one "that can be *administered daily to the patient*." Appx57. Instead, Wyeth distracts by irrelevantly focusing on the meaning of "patient."

achieving the necessary drug concentration in patients to produce the desired therapeutic effect. For example, in pre-trial briefing, AstraZeneca argued for the admissibility of the inventors' 2008 Godin-Heymann publication as directly relevant to enablement and written description because it shows that "the concentrations of HKI-272 used in the patents-in-suit were five-times higher than the maximum tolerated dose, meaning that dose-limiting toxicity would preclude its administration in a therapeutic amount." Appx13312, Appx13321-13322; *see also* Appx17314 (6:11-15). Wyeth complains that AstraZeneca used the term "toxicity" rather than "lethality," Br.61, but this is irrelevant semantics. The district court held that Wyeth's patents fail to enable unit dosing in part because dose-limiting toxicity precluded dosing that could produce the desired therapeutic effect. *E.g.*, Appx61 ("[W]here there is no non-toxic therapeutic range for a given compound, a POSA would not be able to practice the claimed method."). The court's further observation that a toxic dose could be "at the extreme, a fatal dose," Appx57, is correct and does not render the court's judgment defective. *See Adams v. United States*, 59 F.4th 1349, 1355 (Fed. Cir. 2023) ("[W]e review judgments, not opinions.").[7]

[7] Wyeth's caselaw is nothing like this case. In *Astellas Pharma v. Sandoz*, the district court improperly held the patent-at-suit invalid under §101 where the defendant had never advanced any argument under that provision. 117 F.4th 1371, 1376 (Fed. Cir. 2024). Here, however, there is no dispute that throughout the proceedings below AstraZeneca argued the patents lack enablement and written-description support under §112.

The district court correctly concluded that the specification does not enable a POSA to administer the full scope of claimed "unit dosages" to treat gefitinib-resistant NSCLC "*in a patient*." Appx55-63. As noted above, even Wyeth's expert admitted this required avoiding toxic dosing, Appx17548 (939:24-940:5), and during prosecution Wyeth itself distinguished the unit dosage of the claims from prior art "overdosing," which Wyeth argued could not be tolerated by patients on a daily basis, *e.g.*, Appx37076-37077; Appx37415.

The patents provide no guidance on how to determine the claimed unit dosage for administration to patients. The specification describes no working example of the claimed methods of treating; the specification fails to provide even a single example of a compound administered to treat a patient with gefitinib-resistant NSCLC. Appx58-59.

The only examples in the specification are *in vitro* laboratory experiments reporting the activity of three irreversible EGFR inhibitors. Appx207 (7:26-36); Appx17396 (333:25-334:5); Appx17484 (683:13-684:14). As Dr. Haber conceded, prediction of clinical dosing from *in vitro* studies is extremely challenging. Appx17396 (334:6-8). The *in vitro* studies in the patent do not enable a POSA to calculate any unit dose for administration to a patient. Appx15149-15150 (131:1-4) (inventor Dr. Sordella: "I don't think that anybody would be able to infer from this type of experiment what is the exact concentration that you would be able to use in

a patient."); *see also* Appx17482 (677:11-678:13); Appx15139 (45:12-18); Appx15145 (110:2-11).

The lack of enablement is confirmed by the inventors' subsequent inability to find a unit dosage for even the inhibitors identified in the patents. At the time the inventors filed their patent application, they did not know how much of any of the irreversible EGFR inhibitors they were studying *in vitro* could be administered to patients. Appx17396 (336:1-21) (Haber). Once those inhibitors were studied in patients, they learned that the concentrations reported in the patents were many times higher than the maximum tolerated dose for the drug. Appx17396 (336:22-337:9); *see also* Appx17548-17549 (942:10-13, 943:1-22).[8] In Dr. Haber's words, "[t]he concentrations in the test tube are higher than can those you can give to patients." Appx17398 (339:8-11). The inventors' conclusion in 2008 was that:

> [T]he effectiveness seen with this drug [HKI-272] at concentrations required *in vitro* may not be achievable in patients due to drug toxicity, and hence, HKI-272 might not effectively inhibit EGFR T790M at a clinically achievable concentration.

Appx11807. That the inventors were not able to find a unit dosage even for the irreversible EGFR inhibitors identified in the patent clearly demonstrates the undue

[8] As Dr. Haber acknowledged, the maximum tolerated dose is "the most you can administer to patients therapeutically." Appx17396 (334:20-23).

experimentation required to carry out the full scope of the claims, which would require determining a unit dosage for the entire class of irreversible EGFR inhibitors.

Indeed, the patents here claim the use of a wide range of different compounds—specifically any compound that irreversibly inhibits EGFR and binds as specified. Appx205 (3:57-59). The patents thus must enable a POSA to determine a "unit dosage" not just for the inhibitors identified in the patent, but for the full range of claimed inhibitors. Determination of the dosing for even a single compound is unpredictable and requires significant experimentation. Appx17455-17456 (569:17-571:13); Appx17481-17484 (674:8-683:5). A POSA here would need to screen each and every possible inhibitor to determine the "unit dosage" for that inhibitor and to screen out those inhibitors for which no such dose exists because of dose-limiting toxicity. The patents provide no guidance for these determinations. Appx60-61. Carrying out the full scope of the claimed invention instead requires a POSA to engage in extensive trial-and-error to determine which irreversible inhibitors can be administered in a daily unit dosage and what the dosage is. This fails to enable under §112 as a matter of law. *See Amgen*, 598 U.S. at 614 ("calling on scientists to create a wide range of candidate antibodies and then screen each" does not enable as a matter of law); *Baxalta*, 81 F.4th at 1366.

Wyeth first argues that its patents are enabling based on what it calls "the mountain of inventor testing, clinical data, animal testing, and laboratory studies."

Br.47. But this so-called "mountain," as it concerns ***gefitinib-resistant NSCLC***, is comprised entirely of *in vitro* studies in cell lines, Appx17396 (333:20-334:5), and it is "extremely challenging" to determine clinical dosing from *in vitro* studies, Appx15129 (133:13-15). As Dr. Sordella conceded about the *in vitro* testing in the patent, "this is an assay that has been done in a cell culture using completely artificial condition, respect what cells are exposed to in a tumor…. So you don't know, for example, in this case what is the pharmacodynamic, pharmacokinetic of this compound. You don't know how stable are in circulation, how easy are clear from the body, what is the maximum concentration that you can achieve in the serum of these cells." Appx15149 (129:19-130:20); *see also* Appx15129 (134:18-135:9). The record establishes that *in vitro* experiments do not model physiological conditions and do not allow a POSA to determine the dose calculated to produce the desired therapeutic effect, or even whether drug toxicity will preclude such dosing. *E.g.*, Appx17482 (677:11-678:13); Appx17483 (681:9-17); Appx15145 (110:2-24).

As to the purported "mountain" of clinical data, Wyeth identifies no clinical data concerning dosing in patients with gefitinib-resistant NSCLC. The patent discloses none. Similarly, none of the prior art Wyeth cites addresses the issue that the concentrations necessary to inhibit gefitinib-resistant NSCLC may far exceed

what can be administered to patients to produce a therapeutic effect. Appx17397 (336:22-337:3).[9]

Moreover, as discussed above, Wyeth distinguished the prior art describing administration of irreversible EGFR inhibitors to patients with gefitinib resistant NSCLC as teaching "overdosing" in contrast to a "unit dosage." *E.g.*, Appx37074, Appx37076-37077; Appx37415. Wyeth thus argued that the prior art taught away from its claimed unit dosage in prosecuting its patents and cannot now rely upon the prior art to provide the missing information for enablement purposes. *See, e.g.*, *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) ("It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.").

Wyeth next argues that "the irreversible inhibitors used to practice the claims share features supporting their tolerability in patients." Br.48. Wyeth cites to the testimony of Dr. Jorgensen, who conceded at trial that his opinion was based on ***not*** considering the "unit dosage" requirement of the claims. Appx17560 (987:14-18). Here too, Wyeth ignores that the relevant question is not whether irreversible EGFR inhibitors have other uses for which toxicity concerns do not arise, but whether

[9] Wyeth mischaracterizes AstraZeneca's experts on this point. *See* Br.39-40. Far from agreeing the prior art disclosed the claimed unit dosage, AstraZeneca's experts demonstrated that if the specification's disclosure were sufficient (it is not), then the prior art's teachings anticipate or render obvious the claimed methods. Appx17459-17461 (586:1-7, 589:1-592:14); Appx17475 (650:16-19); Appx17478 (665:13-18).

Wyeth's patents enable a POSA to determine the dose "calculated to produce the desired therapeutic effect" in gefitinib-resistant NSCLC patients. As discussed above, the record evidence shows that they do not, regardless of whether the irreversible EGFR inhibitors identified in the patent have features that might otherwise support tolerability. Indeed, as noted above, Wyeth's own witnesses conceded the dosing needed to inhibit gefitinib-resistant NSCLC was many times the maximum tolerated dose for the inhibitors of the patent.

Wyeth argues that the inventors' Godin-Heymann publication does not provide evidence "that irreversible inhibitors actually required intolerable concentrations to achieve a therapeutic effect." Br.49. This argument is foreclosed by the trial record. Wyeth's expert, Dr. Hausheer, conceded that the inventors discovered in Godin-Heymann that "the concentrations being used in the experiments in their patent were higher by a factor of 5 than the maximum tolerated dose." Appx17548 (942:10-13); *see also* Appx17549 (943:2-6) ("What the named inventors said in 2008 is using the maximum tolerated dose, you couldn't effectively inhibit T790M."). Dr. Haber similarly acknowledged that, after filing the patent application, "[he] later found out… that the concentrations that [he was] studying and reporting in [his] patent were five times higher than the maximum tolerated dose for HKI-272." Appx17397 (336:22-337:1). Wyeth's attempt to re-write Godin-Heymann is refuted by the clear trial record.

Even were it not foreclosed Wyeth's argument would still be wrong. Wyeth suggests Godin-Heymann is about "HKI-272 resistance," not gefitinib resistance. Not so. As it states: "all of the HKI-272-resistant clones were cross-resistant to both gefitinib and erlotinib, suggesting that the acquired resistance does not specifically reflect a mechanism unique to irreversible inhibitors." Appx11806. It is for this reason that the inventors recognized (in 2008) that their earlier work (disclosed in the specification) showing irreversible inhibitors to inhibit growth of gefitinib-resistant NSCLC *in vitro* would not translate to clinical use: "it is possible that HKI-272 can overcome T790M only at relatively high doses that are not possible to safely achieve in patients…. Our findings suggest that the effectiveness seen with this drug at concentrations required *in vitro* may not be achievable in patients due to drug toxicity." Appx11807; *see also* Appx15130 (145:2-8) (Haber). The inventors repeated this conclusion in other publications. *E.g.*, Appx39669, Appx39679; Appx39650, Appx39656; *see also* Appx17453-17454 (560:24-565:1).

Wyeth argues that the *in vitro* experiments in the specification show that HKI-272 could be administered in a unit dosage because the compound showed greater activity than gefitinib against cells harboring a T790M mutation. *See* Br.49-50. Dr. Sordella expressly acknowledged that Figure 4b in the patent (which Wyeth cites for this argument, Br.50) reports *in vitro* experiments using "completely artificial conditions" that do not permit a conclusion about clinical dosing. Appx15149-15150

(129:07-131:04). As discussed above, when the inventors studied HKI-272 at concentrations that approximated those that could be achieved in patients, gefitinib-resistant NSCLC cells were not inhibited.

Nor would the specification's description of HKI-272's EGFR-IC_{50} guide the POSA to a unit dosage for that compound, much less any other claimed compound. An IC_{50} is the amount of compound necessary to inhibit 50% of the activity of a protein in an *in vitro* study. Because IC_{50} is a report of *in vitro* activity, it does not provide a basis to determine a dose calculated to produce the desired therapeutic effect in patients. In Dr. Sordella's words, it does not provide "the pharmacodynamics, the pharmacokinetics of the compound" nor does it provide information about bioavailability or drug metabolism or "what is the maximum concentration you can achieve in the serum." Appx15149 (130:13-20).

C. The District Court Did Not Change Its Claim Construction Post-Verdict

Finally, Wyeth incorrectly accuses the district court of changing its construction of "unit dosage" in its JMOL ruling. Br.53-57. Not so. The court throughout the proceedings construed "unit dosage" as Wyeth requested: an amount "calculated to produce the desired therapeutic effect." As noted above, Wyeth requested, and the court agreed, that the term be given no further construction.

Throughout the case, AstraZeneca adduced evidence that the claims are not enabled under the court's construction because (among other things) the

unpredictability around bioavailability and drug toxicity meant undue experimentation was required to determine the dose calculated to produce the desired therapeutic effect. *See, e.g.*, Appx11368 (¶¶407, 411).

In response, Wyeth filed a pretrial motion asking the district court to preclude AstraZeneca's evidence, such as the 2008 Godin-Heymann publication, on the basis that toxicity was, in Wyeth's view, irrelevant to the claimed "unit dosage." Appx17314 (8:8-24) (Wyeth's counsel arguing that Godin-Heyman and "dose-limiting toxicity" are irrelevant to "unit dosage"). The court disagreed, ruling the evidence admissible. In the court's words, "if there's studies that show that when you try to do what the patent tells you to do you can't get the desired therapeutic effect, even if it's the one that the plaintiffs' experts are saying," it is relevant because "the bottom line is if it doesn't work, then you can't make it." Appx17315 (11:14-23). Wyeth thus had fair notice before trial that evidence of dose-limiting toxicity in patients was relevant to determination of the "unit dosage" of the claims. The court did not change its construction post-verdict.[10]

Wyeth also argues that the district court's recognition that the asserted claims require administration "to the patient," Appx57, amounts to a reconstruction of the

[10] In actuality it is Wyeth that has changed its position. Below, Wyeth argued against further construction of "unit dosage." Appx1130; Appx2437. Only now, having lost below, does it seek further construction to exclude consideration of dose-limiting toxicity. But it has forfeited any such request by arguing against further construction below.

"unit dosage" term, *see* Br.54. This too is wrong. The court held the preambles of the claimed methods to be limiting during claim construction and accordingly instructed the jury. Appx141. There was never any confusion that the claimed methods require the desired therapeutic effect "in a patient." Indeed, during the pre-trial hearing related to Wyeth's motion, Wyeth's counsel acknowledged that "the patents are directed to producing [the] effect ***in the cancer patients***." Appx17315 (10:16-17) (emphasis added).

Wyeth's caselaw is wholly different. In *Wi-Lan v. Apple*, for example, the district court expressly acknowledged in its JMOL decision that the pre-trial claim construction did not specifically provide for an element that the court concluded was required post-trial. 811 F.3d 455, 464 (Fed. Cir. 2016) (The district court, "[w]hile acknowledging that its construction 'does not specifically provide for a complex multiplier'," "nevertheless found such a component required."). Here, by contrast, nothing has been added to the court's construction. Before and after trial, the construed claims required daily administration of a "unit dosage" to treat gefitinib-resistant NSCLC "in a patient." Applying this construction, the court correctly concluded that the asserted claims are not enabled as a matter of law.

II. Wyeth Fails to Show Error in the District Court's Determination that the Claimed Methods of Treating Lack Written-Description Support

Wyeth makes no independent argument supporting its appeal of the district court's judgment that the claims lack written-description support in the specification.

Instead, Wyeth argues that the court's written-description judgment should be reversed "for the reasons" set forth in its enablement argument. Br.57.

But the written-description requirement is distinct from enablement and requires a separate analysis. *E.g., Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1377 (Fed. Cir. 2017) ("[T]o satisfy the statutory requirement of a description of the invention, it is not enough for the specification to show how to make and use the invention, i.e., to enable it."); *Novozymes v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013) (affirming JMOL because patentee's enablement argument "misses the point" of the written-description requirement). As the district court recognized, "[t]he test for the sufficiency of the written description is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Appx64 (quotations omitted).

The district court determined that Wyeth's specification fails to show possession of the claimed methods of treating comprising daily administration of a unit dose of an irreversible EGFR inhibitor. In the court's words, "nothing in the specification suggests that the inventors in fact had identified a unit dosage of the specified compounds that could be administered daily to a patient at levels high enough to show the desired therapeutic effect of interfering with the EGFR pathway and killing cancer cells." Appx66-67. Wyeth never addresses this determination;

instead, the entirety of its argument is that "the court failed to credit the specification's disclosures as read by a skilled artisan." Br.57. Wyeth's perfunctory assertion puts AstraZeneca in the unfair position of responding to an argument Wyeth presumably intends to make only in reply. Wyeth's challenge should be denied on this basis alone. *See, e.g.*, *Smithkline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006) ("[M]ere statements of disagreement with the district court as to the existence of factual disputes do not amount to a developed argument.") (collecting cases); *see also Tolbert v. Queens College*, 242 F.3d 58, 75 (2d Cir. 2001) ("It is a settled appellate rule that issues adverted to in a perfunctory manner, unaccompanied by some effort at developed argumentation, are deemed waived.") (cleaned up).

In any event, the district court's conclusion that Wyeth's patents do not contain adequate written-description support for the claimed methods of treating is correct and should be affirmed. Wyeth does not challenge the court's determination that "the specification did not disclose any working examples of unit dosages administered *to patients*." Appx58-59. The sole description of patient dosing in the specification is broad ranges of possible doses, of which the narrowest is 2-500 mg. Here too, "unrebutted evidence" showed 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. Thus, as the court explained, "[a]lthough the specification discusses a suggested range for a unit dosage between 2 and 500 milligrams per day, nothing in the specification suggests that the inventors in fact had identified a unit dosage of the specified compounds that could be administered daily to a patient at levels high enough to show the desired therapeutic effect of interfering with the EGFR pathway and killing cancer cells." Appx66-67. In other words, the specification fails to demonstrate that the inventors were in possession of the claimed method, which requires "administering daily to the patient…a unit dosage."

Tellingly, Wyeth does not cite the specification's description of patient dosing ranges in its written-description argument (to the degree it makes one at all). Instead, Wyeth cites only the specification's description of the EGFR-IC_{50} values for the three irreversible EGFR inhibitors of the claims. Appx57 (citing Appx211(16:77-22)). But this just reports the potency of the inhibitors against EGFR *in vitro*. It sets forth no dosing in patients, let alone a dose "calculated to produce the desired therapeutic effect" in gefitinib-resistant NSCLC patients, as required by the claim. The absence of any disclosure of a unit dosage for carrying out the claimed invention demonstrates that the inventors were not in possession of their claimed method. *See, e.g.*, *Biogen Int'l GmbH v. Mylan Pharm.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021) ("[T]he specification's focus on basic research and broad DMF-dosage ranges show

that the inventors did not possess a therapeutically effective DMF480 dose at the time of filing in 2007.").

As discussed above, the trial record is clear that the *in vitro* studies in the specification would not enable a POSA to determine a unit dosage. As one of the inventors admitted, *in vitro* studies are conducted in "completely artificial" conditions and provide no information about pharmacodynamics, pharmacokinetics, drug absorption, metabolism, or toxicity; it is not possible to determine a therapeutic dose from *in vitro* studies. Appx15149-15150 (129:7-131:11) (Sordella); *see also* Appx17477 (656:9-10) ("[I]t's hard to know equivalence of what you see in a laboratory test tube to what is the actual dose in a human."); Appx17482-17483 (677:18-679:3).

Even were it possible to determine dosing from *in vitro* studies, the patents' disclosure would still not provide written-description support, as the specification does not connect the reported EGFR-IC_{50} values with patient dosing, let alone explain how to calculate a "unit dosage" from that information. That is, it does not show possession of the claimed unit dosage. A claimed invention must be disclosed in the specification "as an integrated whole rather than as a collection of independent limitations." *Novozymes*, 723 F.3d at 1349. A patentee cannot use "an amalgam of disclosures plucked selectively" from the specification to meet the written-description requirement. *Id*.

Here, Wyeth points to its patents' description of EGFR-IC_{50} information plucked from a section of the specification entitled "Generation of Gefitinib-Resistant Cell Lines with Susceptibility to Irreversible Inhibitors." Appx211 (15:52-53). As the title suggests, nothing in that section describes patient dosing. Rather, it is entirely directed to the creation and testing of resistant cell lines *in vitro*.

By contrast, the definition of "unit dose" and the perfunctory reference to patient dosing is in an entirely separate section, entitled "Method of Treating a Patient." Appx207-208 (7:24, 8:59-66, 9:33-38). Strikingly, Wyeth does not identify any portion of this section as showing possession of the claimed unit dosage. This section never references IC_{50} information nor suggests determination of patent dosing from *in vitro* studies. Wyeth's attempt to concoct written-description support for its claimed methods of treating by relying on unrelated disclosure scattered across different parts of the specification fails as a matter of law. *Novozymes*, 723 F.3d at 1349; *see also Flash-Control, LLC v. Intel Corp*., 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021) ("A patent owner cannot show written-description support by picking and choosing claim elements from different embodiments that are never linked together in the specification.").

Moreover, Wyeth's patents contradict the use of *in vitro* data for calculating a unit dosage by instructing that patient-specific information is relevant to dosing: "[t]he skilled artisan is aware of the effective dose for each patient, which may vary

with disease severity, individual genetic variation, or metabolic rate." Appx207 (8:57-59). Such boilerplate is insufficient to show possession (and contradicted by Wyeth's argument during prosecution that the prior art taught "over-dosing" that led a POSA away from the claimed "unit dosage"). *See, e.g.*, *D Three Enters., LLC v. Sunmodo Corp.*, 890 F.3d 1042, 1051 (Fed. Cir. 2018) ("[B]oilerplate language" about the knowledge of a POSA "is not sufficient to show adequate disclosure.").[11] At the same time, the patents' assertion that dosing is patient-specific, depending (among other things) on genetic variation and metabolism, contradicts Wyeth's assertion that a POSA could determine patient dosing from *in vitro* data, and instead confirms that the inventors were not in possession of the claimed "unit dosage" on the basis of the reported EGFR-IC_{50} values.

The lack of written description is confirmed as well by the inventors' own testimony. This Court has made clear that inventor testimony may illustrate the absence of written description. *Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1381 (Fed. Cir. 2019) ("Although inventor testimony cannot establish written-description support where none exists in the four corners of the specification, it illuminates the absence of critical description in this case."); *Idenix*, 941 F.3d at 1164 (citing admission of inventor that claimed sub-

[11] As this Court has explained, "if the disclosure of [the claim elements] were so clearly within the skill of the art, it would have been expressly disclosed in the specification, and in the usual detail." *Genentech*, 108 F.3d at 1367.

genus was only conceived after priority document in support of holding no written description as a matter of law). This makes sense: "one cannot describe what one has not conceived." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

Here, Dr. Haber admitted that, at the time the patent applications were filed, he did not know the amount of the identified irreversible EGFR inhibitors that could be therapeutically administered to patients. Appx17397 (336:1-21). Only after filing the application did the inventors pursue "a clinical trial to determine a dose." Appx17397 (336:5-6). Dr. Kwak, another inventor, similarly testified that determining the dose of an EGFR inhibitor required to achieve a therapeutic effect requires "looking at the preclinical data and the clinical data." Appx15139 (73:4-10). And, as noted above, Dr. Sordella agreed that *in vitro* work was insufficient to determine dosing in patients. Appx15149-15150 (129:07-131:11).

Moreover, three years after filing the patent application, the inventors acknowledged in the Godin-Heymann publication that the "the effectiveness seen with this drug [HKI-272] at concentrations required *in vitro* may not be achievable in patients due to drug toxicity," Appx11807, confirming they were not in possession of a dose calculated to produce the desired therapeutic dose in patients from their *in vitro* work. Dr. Haber conceded as much. Appx17397 (336:12) ("Phase 1 of the clinical trial is to find the dose."); Appx17397 (337:1-3) ("You test the dose in the lab and you see what works, and then you see what can work in patients.").

The sole trial testimony asserting a connection between EGFR-IC_{50} and dosing is the bald statement by Wyeth's expert, Dr. Hausheer, that "we use the IC50 to come up and optimize the unit dose in patients." Appx17520 (828:25-829:1). Dr. Hausheer did not explain how he uses IC_{50} values to "come up with" the unit dose, let alone whether a POSA would know how, and did not explain how the specification's disclosure of EGFR-IC_{50} values for three inhibitors would demonstrate possession of a unit dosage for the full range of irreversible EGFR inhibitors covered by the claim. *See* Appx64 (claims are directed to "an entire class of irreversible EGFR inhibitors that are capable of performing a specific function") (quotation omitted). Such conclusory expert testimony is insufficient to support a jury finding. *See MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1172 (Fed. Cir. 2015) (claim invalid as a matter of law: "Conclusory statements by an expert…are insufficient to sustain a jury's verdict.").

To be sure, clinical testing is not an invariable prerequisite to patentability. However, "when the inventor expressly claims that result, our case law provides that that result must be supported by adequate disclosure in the specification." *Nuvo Pharm.*, 923 F.3d at 1384. Here, Wyeth amended its claims to require daily administration of a dose "calculated to produce the desired therapeutic effect" in patients and distinguished the prior art as disclosing dosing too high ("overdosing") to be tolerable as a daily dose. Appx37074, Appx37076-37077; Appx38609;

Appx37415; Appx39328-39330. The written-description requirement demands that the specification demonstrate possession of the full scope of the methods of treating as claimed, including the unit dosage. As this Court has cautioned, "the law is clear that a patent cannot be awarded for mere theoretical research without more. The written-description requirement limits patent protection only to individuals who perform the difficult work of producing a complete and final invention featuring ***all its claimed limitations*** and publicly disclose the fruits of that effort." *Biogen*, 18 F.4th at 1344 (affirming lack of written description for claimed method of treating because the specification did not show inventors' possession of the claimed therapeutic dose) (emphasis added).

III. Alternatively, the District Court's Judgment Should Be Affirmed Because the Specification Does Not Adequately Support the Claimed Genus of Inhibitors Under § 112

The district court's judgment of invalidity should also be affirmed because the claims are not enabled and lack written description as to the functional class of compounds covered by the claims. The inventors identified three structurally related compounds for use in the claimed method of treating, but Wyeth's claims capture a broad, functionally defined and structurally diverse class neither taught nor described in the specification. This strategy runs afoul of the enablement and written-description requirements.

A. Undue Experimentation Would be Required to Use the Full Scope of Claimed Irreversible EGFR Inhibitors

The patents-in-suit claim the use of any compound, regardless of structure, that (1) irreversibly inhibits EGFR, and (2) covalently binds to a particular location. This Court has repeatedly held that claims directed to a genus of compounds defined by their function and binding targets, rather than their structure, lack enabling support as a matter of law. *See, e.g.*, *Baxalta*, 81 F.4th at 1366-67; *Idenix*, 941 F.3d at 1165.

Here, the trial record confirmed that the genus of irreversible EGFR inhibitors encompassed by the asserted claims is vast, comprising a diverse range of structures. *See* Appx17447 (535:8-20, 537:9-18); Appx17560-17561 (990:17-991:1, 991:20-992:2, 992:8-11). AstraZeneca's expert Dr. Reider explained that the genus of structures with the potential to achieve both claimed functions is ***at least 218 billion unique compounds***. Appx17447 (535:8-20, 537:9-18). Though Wyeth's expert Dr. Jorgensen testified that billions is an "exaggeration," he tellingly did not provide an alternative scope, and Dr. Jorgensen admitted that he previously testified that the '008 patent—a patent cited in the specification as teaching claimed compounds—***describes trillions of irreversible compounds***, Appx17560-17561 (990:17-991:1, 991:20-992:2, 992:8-11); *see also* Appx210 (13:50-51). Regardless of the precise number, the only reasonable conclusion based on the trial evidence is that the claimed genus of inhibitors is enormous. *See Idenix*, 941 F.3d at 1157 (the scope of

claimed compounds, even if "significantly smaller" than billions, was extraordinarily broad and not enabled).

In contrast to the vast scope of the functional claims, there is a dearth of disclosure in the specification. Each of the three compounds identified in the specification shares the same general structural features—the same core, same active warhead, and same chlorine substituent—with only minor structural differences. Appx193 (Figure 2B), Appx205 (3:56-59); Appx207 (7:26-36); Appx17441 (512:14-20); Appx17457 (575:5-13).

Trial evidence demonstrated that the specification's three species do not provide guidance as to the full scope of the structures within the claimed genus. Wyeth argues that the patents encompass the accused Tagrisso compound, but its structure is meaningfully different from the specification's compounds, Appx17441 (512:21-513:13); Appx15231. Wyeth's experts admitted that Tagrisso's structure is not taught by the specification. *See* Appx17396 (333:5-7); Appx17479 (663:4-14). The trial record makes clear what the examiner recognized during prosecution: Tagrisso is structurally and pharmacologically distinct from the broadly claimed class of irreversible inhibitors. Appx37310-37311; *see also* Appx17453 (559:21-560:20).

The specification leaves the POSA to undertake the extraordinarily onerous and unpredictable task of ***making and testing each inhibitor***, Appx17447 (535:12-

539:19); Appx17455 (567:12-568:21), in a "highly unpredictable" art, Appx36977. Such trial-and-error fails to provide adequate enablement as a matter of law. *See, e.g.*, *Amgen*, 598 U.S. at 613-14 (specification's instruction to engage in trial-and-error is not enabling, even if a POSA could subsequently "make and use every undisclosed but functional [embodiment]"); *Idenix*, 941 F.3d at 1161 ("It is not enough to identify a target to be the subject of future testing. A specification that requires a POSA to engage in an iterative, trial-and-error process to practice the claimed invention does not provide an enabling disclosure.") (cleaned up).

The district court improperly credited Dr. Jorgensen's conclusory opinion that knowledge and experience would allow a POSA to limit the number of potential compounds based on certain features required to bind to EFGR. Appx49-50. But he did not explain how those limitations narrow the scope of possible compounds such that undue experimentation would not be required to make and use the full scope of the claimed compounds. *Amgen*, 987 F.3d at 1087-88 (affirming JMOL of non-enablement for class of functionally defined antibodies in part because of the "conspicuous absence of nonconclusory evidence that the full scope of the broad claims can predictably be generated by the described methods"). Nor is it consistent with the teachings of the specification, Appx210 (13:3-13) (expressly instructing the use of large compounds that Dr. Jorgensen asserted would be deemed unsuitable by a POSA, Appx17557 (977:21-24)).

The district court suggested that Dr. Jorgensen's testimony described a "general quality" or "rule" that would allow a POSA to practice the claimed method. *See* Appx50-51 (citing *Amgen*, 598 U.S. at 611-12). But the court conspicuously fails to identify this "general quality," and neither Dr. Jorgensen nor any other witness identified any language in the specification describing an alleged structure-function relationship. *See Amgen*, 598 U.S. at 611 ("It may suffice to give an example if ***the specification*** also discloses 'some general quality'…."). Merely identifying a ***function*** (such as irreversible inhibition) does not constitute such a general quality; instead, the specification must disclose a general quality that permits a POSA "to predict" which claimed agent "will perform the claimed functions." *Baxalta*, 81 F.4th at 1366. The specification here lacks any such disclosure.

Nor can Wyeth rely on a POSA's knowledge to remedy the specification's deficiencies. *E.g.*, *Idenix*, 941 F.3d at 1161 ("A patent owner is required to provide an enabling disclosure in the specification; it cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information."); *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) ("The deficiencies in the description as to enablement cannot be cured in this case by looking to the knowledge of those skilled in the art at the time of the invention.").

In any event, a POSA's general knowledge of irreversible EGFR inhibitors would have been insufficient to guide a POSA to those inhibitors capable of

functioning as required, as exemplified by the inventors' own failure to identify a such an inhibitor. *Supra*. Moreover, even were a POSA able to make and use "some" or "a handful" of irreversible EGFR inhibitors, as Dr. Jorgensen suggested, *see* Appx17558 (982:16-983:12), the specification would nonetheless fail to enable the full scope of the asserted claims, *e.g.*, *Idenix*, 941 F.3d at 1161-62; *Enzo*, 928 F.3d at 1349 (one working embodiment did not enable the many other embodiments within the scope of the functionally defined claims). The undue amount of experimentation required to make and use the full scope of the claimed EGFR inhibitors renders the asserted claims not enabled as a matter law. *See, e.g.*, *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385 (Fed. Cir. 2013).

B. A POSA Would Not Understand the Inventors to be in Possession of the Full Scope of Claimed Inhibitors for Use in the Claimed Methods

A POSA would not understand the specification to convey that the inventors were in possession of the vast functional genus of compounds that could be used to carry out the claimed methods. The lack of written description is demonstrated by the failure of the specification to describe any such range of compounds, including compounds that are either functionally or structurally like the wild-type sparing, mutant-selective inhibitor, Tagrisso, that Wyeth asserts falls within the claims.

This Court has made clear that "a sufficient description of a genus...requires the disclosure of either a representative number of species falling within the scope

of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Abbvie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1299 (Fed. Cir. 2014). Here, the specification does neither. For example, it is undisputed that Tagrisso contains both a different core and a different warhead than the inhibitors identified in Wyeth's patents. Appx17741 (512:21-513:13); Appx15231.

In determining adequate written description, the district court relied on Dr. Jorgensen's testimony that the differences between the disclosed inhibitors and Tagrisso were minor. Appx65. This misses the point of the written-description analysis. Dr. Jorgensen acknowledged that Tagrisso's core and warhead were different, and while he asserted that the differences were minor because the structures in Tagrisso were purportedly commonly used in medicinal chemistry, he never explained how that meant a POSA would understand ***from the specification*** that the inventors were in possession of the full scope of the genus. *See Novozymes*, 723 F.3d at 1350 ("The question before us is not whether [a POSA] presented with the 2000 application would have been enabled to take those final steps, but whether the 2000 application 'discloses the [variants] to him, specifically, as something appellants actually invented.'"). Indeed, here too, Dr. Haber conceded that they did not invent third-generation EGFR inhibitors like Tagrisso. Appx15129-15130 (143:23-144:06).

Neither Dr. Jorgensen nor the district court ever connected the disclosure of the specification to the full scope of the claimed genus. That disclosure contradicts possession of the full genus. For example, the specification identifies the preferred irreversible EGFR inhibitors by structural class ("4-anilinoquinoline-3-carbonitriles") and suggests three other classes as "promising" inhibitors. Appx207 (7:24-36); Appx204 (2:62-64). Tagrisso and other mutant-specific EGFR inhibitors do not fall within any of these classes. Dr. Jorgensen's conclusory assertion that the differences in core and warhead are "minor" cannot establish written-description support, as Tagrisso indisputably falls outside the specification's disclosure even with regard to those structural characteristics the inventors elected to call out in the specification. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("It is not sufficient for purposes of the written-description requirement of § 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose.").

Moreover, it is undisputed that (unlike Tagrisso) all the EGFR inhibitors identified in the specification were designed to target wild-type EGFR like all first- and second-generation inhibitors. Appx17441; Appx17453 (514:5-6, 561:16-562:4); Appx15141 (180:18-181:06); Appx39674; Appx39657. It is also undisputed that the specification does not describe the wild-type sparing, mutant-selective profile like

Tagrisso. Appx15130 (145:13-22); Appx17453 (559:21-562:6); *see also* Appx17560 (989:7-22, 990:4-8). Indeed, ***the inventors recognized*** that Tagrisso's mutant-selective profile was a true advancement and the key to treating gefitinib-resistant patients. *See* Appx15131-15132 (172:4-12, 178:6-12); Appx39624-39625; Appx39678-39680; Appx39656-39657. Tagrisso is thus also functionally distinct from the inhibitors disclosed in Wyeth's patents.

Dr. Jorgensen's testimony focused on creating an irreversible inhibitor that is irreversible *in vitro*, Appx16035-16036 (982:20-983:12), but merely creating an inhibitor that is irreversible *in vitro* is not sufficient for the claimed methods. The claimed methods require an irreversible EGFR inhibitor that can reach cells "in a patient" and irreversibly bind EGFR. *See* Appx2430-2435. Here, Dr. Jorgensen provided no testimony demonstrating that a POSA would understand the inventors to possess such inhibitors. Nor did Wyeth provide evidence that function can be predicted by structure.

The only reasonable conclusion to draw from the evidence presented at trial is what the inventors recognized—the true advancement in treating gefitinib-resistant NSCLC came with the development of Tagrisso. Where a patent identifies a "problem to be solved while claiming all solutions to it...covering any compound later actually invented and determined to fall within the claim's functional

boundaries," the specification fails to demonstrate possession. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021) (cleaned up).

IV. The District Court Correctly Determined that Wyeth is Not Entitled to Pre-Issuance Damages Under § 154(d)

If this Court affirms the district court's judgment, it need not reach whether Wyeth was correctly denied pre-issuance damages. Regardless, pre-issuance damages under §154(d) are impermissible here because they are not available for induced infringement, and because the asserted claims are not "substantially identical" to the published patent applications.

A. Section 154(d) Provides No Basis for Induced-Infringement Damages

Wyeth accused AstraZeneca only of induced infringement under §271(b). The district court correctly held that pre-issuance damages under §154(d) are not available for claims of inducement. Appx103-105. Section 154(d) expressly defines the scope of pre-issuance remedies ("provisional rights") and limits them to the acts of direct infringers. 35 U.S.C. § 154(d). Wyeth's argument that "[n]othing in subsection (d) excludes induced infringement," Br.59, gets it backwards. The Supreme Court warned that courts must narrowly construe remedies and decline to "expand the coverage of the statute to subsume other remedies" beyond those expressly provided by Congress. *Nat'l R.R. Passenger Corp. v. Nat'l Ass'n of R.R. Passengers*, 414 U.S. 453, 458 (1974).

Wyeth asserts that §154(d) is somehow "parallel" to "its sister provision, §154(a)," which Wyeth says also does not exclude inducement. This makes no sense. An action for induced infringement lies in §271(b), not §154(a), and §271(b) applies only to acts taken after patent issuance. *See Nat'l Presto Indus. v. West Bend Co.*, 76 F.3d 1185, 1196 (Fed. Cir. 1996) ("[A]s a matter of law Section 271(b) does not reach actions taken before issuance of the adverse patent."). By contrast, an action for pre-issuance damages lies in §154(d), which by its plain terms does not apply to acts of inducement.[12]

As this Court has recognized, and Wyeth concedes, Br.62-63, Congress intended §154(d) to be a "narrow exception" to the rule that damages do not accrue pre-patent issuance. *Rosebud LMS Inc. v. Adobe Sys.*, 812 F.3d 1070, 1073 (Fed. Cir. 2016). Wyeth's attempt to incorporate all the provisions of §271 into §154(d) would grossly violate this, as it would open pre-issuance damages to all manner of actors, including inducers, contributors, and suppliers of components.

Congress is presumed to have enacted §154(d) "with knowledge of the law," and the statute "is presumed to be harmonious with existing law and judicial

[12] District courts have concluded that §154(d) does not create provisional rights for indirect infringement. *E.g.*, *Worldwide Home Prods., Inc. v. Time, Inc.*, 2012 WL 6705876, at *2 (S.D.N.Y. Dec. 21, 2012); *Sloan Valve Co. v. Zurn Indus. Inc.*, 2012 WL 6214608, at *3 (N.D. Ill. Dec. 12, 2012); *see also Hitkansut LLC v. United States*, 130 Fed. Cl. 353, 368 (2017) (silence to indirect infringement does not waive sovereign immunity for it under §1498).

concepts." *Aectra Ref. & Mktg., Inc. v. United States*, 565 F.3d 1364, 1370 (Fed. Cir. 2009). Congress' choice not to overturn *National Presto* and extend pre-issuance damages to inducers should be respected.

B. The Claims are not "Substantially Identical" to the "Published" Applications

Section 154(d) restricts pre-issuance damages to cases in which the asserted claims are "substantially identical" to those in the earlier "published patent application." 35 U.S.C. § 154(d)(2). There is no dispute that the asserted claims are ***not*** substantially identical to Wyeth's published claims. *Compare* Appx221 *with* Appx20648; *compare* Appx269 *with* Appx38206. Wyeth instead requests pre-issuance damages based on ***unpublished***, pending claims with the applicants' final amendments during prosecution. Appx7413-7414. Unpublished claims do not provide a basis for damages under §154(d).

Section 154(d)(1) provides that any provisional rights "begin[] on the date of publication of the application for such patent under section 122(b)…." Section 122(b)—enacted through the same legislation as §154(d)—provides that, "each application for a patent shall be published…promptly after the expiration of a period of 18 months from the earliest filing date." 35 U.S.C. § 122(b)(1)(A); *see also* 37 C.F.R. §§ 1.215(a), (c) ("[t]he publication" is the as-filed application with claim amendments filed before, not after). Congress's statutory framework is clear:

"publication" in §154(d)(2), refers to a specific patent application with specific claims published on a specific date.

Moreover, permitting Wyeth to recover pre-issuance damages based on its unpublished, pending claims would make §154(d) the rule rather than a "narrow exception." *Rosebud*, 812 F.3d at 1073. If patentees were able to pursue pre-issuance damages based on pending claims, virtually ***all*** claims would be entitled to them.[13]

CONCLUSION

The district court's judgment should be affirmed.

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Respectfully submitted,

/s/ Christopher N. Sipes
Christopher N. Sipes
Einar Stole
Megan P. Keane
R. Jason Fowler
COVINGTON & BURLING LLP
One CityCenter, 850 Tenth St. NW
Washington, DC 20001
(202) 662-6000

Counsel for Defendants-Appellees

[13] Accordingly, district courts have consistently rejected attempts like Wyeth's to expand §154(d) to cover unpublished, pending claims. *Bayer Healthcare LLC v. Baxalta Inc.*, 2019 WL 291143, at *2 (D. Del. Jan. 22, 2019); *Abdou v. Alphatec Spine, Inc.*, 2014 WL 6611422, at *5 (S.D. Cal. Nov. 19, 2014).

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2024-2325

Short Case Caption: Wyeth LLC v. AstraZeneca Pharmaceuticals LP

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