

No. 2024-2325

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**United States Court of Appeals  
for the Federal Circuit**

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WYETH LLC,

*Plaintiff-Appellant,*

v.

ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB,

*Defendants-Appellees.*

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

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**REPLY BRIEF OF APPELLANT WYETH LLC**

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FORM 9. Certificate of Interest

Form 9 (p. 1)  
March 2023

**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

**CERTIFICATE OF INTEREST**

**Case Number** 2024-2325

**Short Case Caption** Wyeth LLC v. AstraZeneca Pharmaceuticals LP

**Filing Party/Entity** Wyeth LLC

**Instructions:**

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

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

Date: 06/06/2025

Signature: /s/ Jennifer L. Swize

Name: Jennifer L. Swize

FORM 9. Certificate of Interest

Form 9 (p. 2)  
March 2023

<b>1. Represented Entities.</b> Fed. Cir. R. 47.4(a)(1).	<b>2. Real Party in Interest.</b> Fed. Cir. R. 47.4(a)(2).	<b>3. Parent Corporations and Stockholders.</b> 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.  <input checked="" type="checkbox"/> 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.  <input type="checkbox"/> None/Not Applicable
Wyeth LLC		Pfizer Inc.
Please see attached for related disclosure.		

Additional pages attached

FORM 9. Certificate of Interest

Form 9 (p. 3)  
March 2023

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

None/Not Applicable  Additional pages attached

Please see attached.		

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

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

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

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

None/Not Applicable  Additional pages attached


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

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

**2. Real Party in Interest:** N/A

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

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

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### Briefs

WBr.	Opening Brief of Plaintiff-Appellant Wyeth LLC (Doc. No. 10)
AZBr.	Response Brief of Defendants-Appellees AstraZeneca Pharmaceuticals LP and AstraZeneca AB (Doc. No. 14)
AmicusBr.	Brief of Regeneron Pharmaceuticals, Inc. and Sanofi-Aventis U.S. LLC as Amici Curiae in Support of Appellees (Doc. No. 22)

### Terms

'008 patent	U.S. Patent No. 6,002,008
'162 patent	U.S. Patent No. 10,596,162
'314 patent	U.S. Patent No. 10,603,314
Agus	Agus, <i>Method of Treating Cancer Using Kinase Inhibitors</i> , WO 03/103676 A2 (2003)
Allen 2002	Allen et al., <i>Potential Benefits of the Irreversible Pan-erbB Inhibitor, CI-1033, in the Treatment of Breast Cancer</i> , 29 Seminars in Oncology (Iss. 3, Supp. 11) 11-21 (2002)
Allen 2003	Allen et al., <i>CI-1033, an Irreversible Pan-erbB Receptor Inhibitor and its Potential Application for the Treatment of Breast Cancer</i> , 30 Seminars in Oncology (Iss. 5, Supp. 16) (2003)
Court	U.S. Court of Appeals for the Federal Circuit
district court, or court	U.S. District Court for the District of Delaware, Judge Matthew F. Kennelly (sitting by designation)
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
Godin-Heymann	Godin-Heymann et al., <i>The T790M "Gatekeeper" Mutation in EGFR Mediates Resistance to Low Concentrations of an Irreversible EGFR Inhibitor</i> , Mol. Cancer Ther. (Vol. 7, No. 4) 874-9 (2008)

IC <sub>50</sub>	half-maximal inhibitory concentration
JMOL	judgment as a matter of law
NSCLC	non-small cell lung cancer
patents	The patents-in-suit: U.S. Patent Nos. 10,596,162 and 10,603,314
POSA	person of skill in the art, or skilled artisan
Stamos	Stamos et al., <i>Structure of the Epidermal Growth Factor Receptor Kinase Domain Alone and in Complex with a 4-Anilinoquinazoline Inhibitor</i> , 277 J. Biol. Chem. (No. 48) 46265-72 (2002)
TKI	tyrosine kinase inhibitor

## TABLE OF WITNESSES

This table, provided for the convenience of the Court, identifies witnesses referenced by name in Wyeth's Reply; it is not a comprehensive list of witnesses called at trial or whose testimony is cited.

### Wyeth's Expert Witnesses

Dr. Hausheer	Dr. Frederick Hausheer, Wyeth's expert in the field of oncology and drug discovery, including non-small cell lung cancer. Appx17375 (249:1-252:22).
Dr. Jorgensen	Dr. William Jorgensen, Wyeth's expert in organic and medicinal chemistry, drug discovery, and molecular modeling. Appx17551 (952:1-954:9).
Dr. Weiss	Dr. Glenn Weiss, Wyeth's expert in the treatment of lung cancer. Appx17350-51 (152:20-155:16).

### AstraZeneca's Expert Witnesses

Dr. Jänne	Dr. Pasi Jänne, AstraZeneca's expert in the treatment of lung cancer. Appx17466-68 (614:18-619:11).
Dr. Reider	Dr. Paul Reider, AstraZeneca's expert in medicinal chemistry and drug development. Appx17438-40 (503:2-508:5).
Dr. Taft	Dr. Robert Taft, AstraZeneca's drug development expert. Appx17480-81 (669:18-671:23).

### Additional Witnesses

Dr. Haber	Dr. Daniel Haber, co-inventor of the patents-in-suit. Appx176; Appx223.
Dr. Kwak	Dr. Eunice Kwak, co-inventor of the patents-in-suit. Appx176; Appx223.
Dr. Rabindran	Dr. Sridhar Rabindran, co-inventor of the patents-in-suit. Appx176; Appx223.
Dr. Sordella	Dr. Raffaella Sordella, co-inventor of the patents-in-suit. Appx176; Appx223.
Dr. Ward	Dr. Richard Ward, executive director of AstraZeneca's oncology business. Appx17380 (270:20-24); Appx17410 (388:16-389:10).

## INTRODUCTION

AstraZeneca’s unit-dosage arguments suffer from three independent failings.

**First**, the record did not establish lack of enablement or written description of any “toxicity” limitation. AstraZeneca does not meaningfully defend the concerns about “fatal” doses that drove the district court’s analysis. Instead, AstraZeneca primarily takes for granted a more nebulous “toxicity” limitation, to argue that the record contains supposedly undisputed evidence of dosages too “toxic” to administer. Part I thus meets AstraZeneca on its own turf, presenting the Court with record-specific grounds to reverse. To start, AstraZeneca’s “toxicity” arguments contradict common sense. Patients facing serious, deadly diseases like NSCLC often choose treatments with even significant side effects. And the jury heard ample evidence that artisans could identify administrable dosages to practice the claims notwithstanding potential side effects.

**Second**, Part II shows that the claims contain no “toxicity” limitation in the first place; imposing one here would contradict decades of precedent epitomized by *United Therapeutics*. Inventors generally need not conduct “toxicity” testing in human subjects to satisfy patenting requirements, and the claims-in-suit fall squarely within that precedent.

**Third**, Part III explains why, even if the evidence were as AstraZeneca says (it is not), and even if the claims contained some kind of “toxicity” limitation (they

do not), JMOL cannot rest on a construction different than the one on which the case was tried. There is simply no daylight between the safety and efficacy requirements that even AstraZeneca acknowledges were properly excluded at trial and the post-trial “toxicity” limitation that AstraZeneca now defends. This additional reason compels reversal (or at least vacatur).

The failure of AstraZeneca’s unit-dosage arguments leaves two more issues for the Court to resolve. Part IV demonstrates that AstraZeneca’s alternative § 112 arguments, just like its evidentiary unit-dosage arguments, rest on erroneous—and, in any event, contested—interpretations of the record. As the district court held, the jury correctly rejected these alternative arguments. And Part V shows why AstraZeneca’s arguments against pre-issuance damages contradict statutory text and context.

## ARGUMENT

### **I. A REASONABLE JURY WAS NOT REQUIRED TO ACCEPT ASTRAZENECA’S UNIT-DOSAGE ARGUMENTS**

The district court deemed the claims invalid under § 112 as a matter of law based on a supposed no-lethality limitation. AstraZeneca offers no meaningful defense of this analysis. It instead seizes on the court’s reference to a nebulous “toxicity” cap. But the evidence did not require a verdict that AstraZeneca met its

burden of proving clearly and convincingly that the patents fail to enable or describe the use of dosages satisfying any such element.<sup>1</sup>

**A. The District Court’s “Lethality” Basis for JMOL Is Unsupported—and Essentially Undefended**

The court overturned the verdict based on “lethality”—its concern that the claimed treatments could kill patients, so the patents needed to teach and describe how to avoid that. Appx57-63; Appx66-67. That fundamentally misapprehends the record. There is *zero* evidence that avoiding fatal doses took too much work—AstraZeneca’s trial presentation and JMOL brief never even suggested as much. WBr.36-45, 57. Rather than hear about dosages that are fatal, lethal, deadly, or the like, the jury heard an array of evidence—including data in the patents, expert testimony, and human and animal testing in other disease contexts—that the patents enable and describe administering unit dosages to patients. WBr.9-12, 38-43, 45-53, 57. The patents themselves expressly state: “The skilled artisan is aware of the effective dose for each patient, which may vary with disease severity, individual genetic variation, or metabolic rate.” Appx207 (8:57-66) (“satisfactory results” at, “preferably,” 2-500 mg).

Tellingly, AstraZeneca only perfunctorily invokes the court’s rationale. Briefly echoing the court’s statement that dosages could be “fatal,” AZBr.33,

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<sup>1</sup> As discussed at WBr.27-36 and Part II, *infra*, the claims contain no such limitation.

AstraZeneca refers at most to a single piece of evidence: the post-filing Godin-Heymann paper, which noted both a completed Phase 1 trial on HKI-272 and other ongoing human trials on irreversible inhibitors—all without mentioning *any* fatalities. Appx39637-42 (also at Appx11804-09). There is simply no evidence supporting the court’s “lethality” concern.

**B. A Reasonable Jury Could Reject AstraZeneca’s “Toxicity” Enablement Argument**

AstraZeneca’s seizure on the court’s reference to “toxicity” fares no better. *E.g.*, AZBr.26, 34-41. If toxicity means something less than lethality, it is side effects. WBr.22, 43-44. And the side effects here are common and manageable: diarrhea, vomiting, rashes, and nailbed issues. WBr.42-44. The record does not support that these side effects would be worse than the disease (drug-resistant lung cancer), nor create too much work for practicing the claims.

As a threshold matter, much of AstraZeneca’s discussion and cited evidence is irrelevant. AstraZeneca focuses on FDA-like testing as key for enablement, but accepts the court’s trial construction that the claims “require neither FDA approval nor clinical effectiveness.” Appx56; AZBr.28; *accord, e.g.*, Appx142 (“This claim term does not require clinical efficacy.”). That construction compelled follow-on evidentiary rulings that AstraZeneca likewise does not challenge, such as precluding FDA standards from being raised at trial: “[N]obody’s going to get to talk about the FDA. I said that now twice.” Appx17315 (10:23-25).

AstraZeneca nonetheless repeatedly invokes FDA and clinical standards as the benchmark for § 112, including the notion that determining a “unit dosage” would require “extensive preclinical and eventually clinical testing” on live human patients. AZBr.16, 34-35, 40, 50; *see also, e.g.*, AZBr.1-3, 14-20, 25, 34-37, 39-41, 45-52. When AstraZeneca did likewise at trial, with its witnesses insisting on *in vivo* trials to ascertain a “unit dosage,” Appx17472 (638:6-17) (Jänne: demanding “a whole program to develop a drug and test it in a patient”); Appx17455-56 (570:20-571:13) (Reider: demanding “Phase 1 trials, and then Phase 2 trials” and then “Phase 3”); Appx17563 (999:19-25) (Taft: “The way that you determine a maximum tolerated dose in patients is ... typically in a Phase 1 clinical trial.”), the court responded by expressly instructing the jury that “unit dosage” “does not require clinical efficacy,” Appx141-42; Appx17523 (841:15-842:16). Since the court’s undisputed construction rendered FDA and clinical standards irrelevant to the jury, AstraZeneca cannot invoke them to overturn the verdict.

To the degree AstraZeneca seeks to operationalize a “toxicity” limitation by some sort of balancing side effects against efficacy, unmoored from FDA and clinical standards (which it can’t use), JMOL remains improper.

Vagueness is one reason. AstraZeneca never specified any meaning of “toxicity.” AstraZeneca accepts that not every side effect would be disqualifying, AZBr.28, but fails to define a threshold. What type or severity of side effects is too

much? Measured by what metric, and by whom? Without confronting these questions, AstraZeneca just bandies around loose notions of “toxicity.” In the face of this nebulous theory, a reasonable jury could easily reject non-enablement.

Common sense—which juries properly apply, Appx127—is another reason the theory fails. “[F]ew pharmaceuticals are free of toxic effects in some circumstances and dosages.” *Mayne Pharma Int’l Pty. Ltd. v. Merck Sharp & Dohme Corp.*, 927 F.3d 1232, 1241 (Fed. Cir. 2019). Side effects—and their inverse, “safety”—are “a relative matter,” “balanc[ed]” by individual patients and doctors against the disease and prognosis. *In re Hartop*, 311 F.2d 249, 255 (C.C.P.A. 1962). Compared to NSCLC, the side effects here are minor—e.g., rashes, gastrointestinal issues. Appx17470 (630:2-14); *see also, e.g.*, Appx18499 (EKB-569 “generally well tolerated with an acceptable ... safety profile” despite “[d]iarrhea and rash”). Tagrisso causes these same issues, Appx17423 (440:16-442:7), and patients with deadly cancers like NSCLC commonly accept treatments that are “quite toxic” with only “modest benefit,” Appx17386 (293:6-15). A jury was not required to accept AstraZeneca’s apparent position that, given such tradeoffs, the side effects here made identification of administrable dosages too difficult.

Moreover, irreversible inhibitors were successfully administered to patients with other diseases. Appx17397 (337:16-21) (Q. “[T]he concentrations of ... EGFR

inhibitors that you're describing in your patent are too high to be administered therapeutically to patients, correct?" A. "No, because the drug actually is being used in patients in other settings."). For instance, Allen 2002—focusing on breast cancer and discussing patients “with a variety of advanced-stage [cancers]”—highlighted the “acceptable” “safety profile” for irreversible inhibitor CI-1033 with “doses ranging from 50 to 750 mg/day” (similar to the patents-in-suit). Appx18191-92; *see also* Appx17460 (589:18-24); Appx39617-18 (Allen 2003, likewise focused on breast cancer, summarizing “acceptable side-effect[s]” for “[d]aily dosages ... from 2mg/d to 1,000 mg/d”). The patents cite Allen 2002 and related studies, which were known to the skilled artisan. WBr.11-12, 29, 38-42.

AstraZeneca attempts to dismiss such evidence because it pertains to other diseases, AZBr.37, but AstraZeneca gave the jury no reason to doubt its relevance. To the contrary, AstraZeneca’s own expert acknowledged that Phase 1 trials can include patients with various diseases, reinforcing the relevance of other cancer settings. Appx17480 (668:4-20) (Taft); *see also* WBr.9-12, 38-43. And as Dr. Haber explained, the side effects of treatment with a compound are the same “whether you have lung cancer, breast cancer, or other cancers.” Appx17398 (339:2-7).

Notwithstanding this evidence, AstraZeneca leans heavily on the Godin-Heymann paper, touting its reference to a “dose-limiting toxicity” for HKI-272 of

0.2 $\mu$ mol/L, Appx39640, as evidence that the dosages used in the claims are higher than “the maximum tolerated dose” and that “the inventors recognized” this. AZBr.39-40. But far from suggesting that irreversible inhibitors cannot be administered or that “attempts to treat patients failed,” AZBr.2, Godin-Heymann is predicated on the notion that irreversible inhibitors are administered to patients and *effective* at killing gefitinib-resistant cells: Godin-Heymann addresses next-generation issues of patients with gefitinib-resistant NSCLC “who *respond* to irreversible inhibitors” but may eventually develop resistance to one of those, HKI-272. Appx39637 (emphasis added). AstraZeneca’s claim that Godin-Heymann is not about HKI-272 resistance, AZBr.40, is implausible on its face, and, in any event, “competing interpretations” of studies are “question[s] of fact” for the jury. *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1347 (Fed. Cir. 2021).<sup>2</sup>

As for Godin-Heymann’s reference to “dose-limiting toxicity,” that concerns legally irrelevant FDA standards from an underlying “phase I clinical study.” Appx39640. And irrelevance aside, Godin-Heymann provides scant information about that study, e.g., no description of its patient population, analysis, or standard

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<sup>2</sup> AstraZeneca’s observation that HKI-272-resistant cells may also resist gefitinib, AZBr.40; Appx39639, is beside the point. The claims treat gefitinib resistance, not HKI-272 resistance. Appx221. The inventors showed that irreversible inhibitors, including HKI-272, treat gefitinib resistance. *E.g.*, WBr.49-50.

it employed, leaving the jury good reason to reject AstraZeneca's speculation. Dr. Hausheer explained why Godin-Heymann's discussion did not change his view and was insufficient to clearly and convincingly prove invalidity under § 112. Appx17550 (949:17-950:24) ("what I would do, ... I would get a copy of the actual study ... there's no reference. It's no citation. I can't go any further ..."). And other literature demonstrated the administrability of irreversible inhibitors as known and tested compounds. WBr.9-12, 38-43. The research the patents-in-suit disclosed reinforces that HKI-272 kills gefitinib-resistant NSCLC—expressly showing this at every concentration tested (including below 0.2µmol/L), further refuting AstraZeneca's use of Godin-Heymann. Appx198 (figure 4B); Appx206 (5:67-6:3); Appx17355 (169:19-170:8) (Weiss).

To manufacture a supposed non-dispute, AstraZeneca says Dr. Hausheer "conceded" its reading of Godin-Heymann. AZBr.39. But there, Dr. Hausheer simply acknowledged what Godin-Heymann literally "said," Appx17549 (943:1-6), while elsewhere making clear he *disagreed* with AstraZeneca's interpretation and inferences, e.g., Appx17548 (941:13-17); *see also* Appx17397 (337:16-21) (Dr. Haber similarly disagreeing). There is no "conceded" reading.<sup>3</sup>

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<sup>3</sup> AstraZeneca's assertion about what the "inventors repeated" "in other publications" is also unsupported. AZBr.40. The inventors stood by their invention of using irreversible inhibitors to kill gefitinib-resistant cells. AstraZeneca's cited testimony is from its own expert, Dr. Reider, not the inventors. Appx17453-54

Finally, AstraZeneca attempts to discount the patents' reporting of the inventors' experiments and EGFR-IC<sub>50</sub> data. AZBr.40-41. The former show that irreversible inhibitors suppress gefitinib-resistant NSCLC across every concentration tested; the latter report concentrations required to inhibit 50% of EGFR activity that are below the supposed maximum tolerated dose of 0.2 $\mu$ mol/L. WBr.49-51. AstraZeneca invokes only Dr. Sordella's characterization of the inventors' experiments (though she nowhere discussed the IC<sub>50</sub> data) as using "completely artificial conditions," arguing this "do[es] not permit a conclusion about clinical dosing." AZBr.40-41. Besides again invoking irrelevant clinical-efficacy standards, AstraZeneca's argument ignores that the inventors reported an "excellent correlation between clinical responsiveness ... and ... cell lines." Appx211 (15:54-57). Indeed, Dr. Sordella *confirmed* that the inventors' use of cells "derived from [NSCLC] patients" "mimic[ked] what was happening in patients." Appx17510-11 (790:4-791:17); Appx15150-51 (132:01-15) ("[T]his experiment strongly suggest ... use of inhibitor with the property of the HKI-272, HKI-357,

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(560:24-565:1). And AstraZeneca's documentary cites are irrelevant. The first does not reference Godin-Heymann; it speculates that "toxicity in skin ... may limit dosing required to effectively suppress EGFR T790M" but notes that "clinical testing" continues. Appx39669-71; *see also* Appx39679 (opining that another irreversible inhibitor, WZ4002, "could potentially affect wild-type EGFR" over "prolonged administration"). The second merely notes a phase 2 trial of HKI-272 that did "not measure[]" T790M inhibition. Appx39650, Appx39656.

EKB-56[9], most likely they would work ... in a patient.”). And as Dr. Hausheer testified, skilled artisans would consider EGFR-IC<sub>50</sub> values “therapeutically important” and useful to “optimize the unit dose in patients” (and optimization is beyond what the patents require). Appx17520 (828:17-829:1). AstraZeneca’s attempt to ignore this testimony does not mean the jury had to do so.

**C. A Reasonable Jury Could Reject AstraZeneca’s “Toxicity” Written-Description Argument**

AstraZeneca similarly failed to carry its burden in challenging written description of not “unduly toxic” doses. WBr.24-25, 57-58.

To start, AstraZeneca’s suggestion of an “independent” issue for written description is wrong. *See* AZBr.43-45. AstraZeneca made no independent argument below. Instead, its unit-dosage written-description argument piggybacked on enablement—even resting on the same contested evidence (via unexplained “*supra*” cites). Appx15695-96.

Scant surprise, then, that the court offered no independent rationale either. Its written-description discussion addressed whether “the inventors in fact had identified a unit dosage ... that could be administered daily to a patient at levels high enough” to kill cancer cells. Appx66-67. This is the same fact question—whether “the dosage level required for the compounds to be therapeutically effective could be unduly toxic to a patient”—that underpins the enablement dispute, as the court recognized. Appx59; Appx67 (“as the Court discussed with respect to

enablement...”). Wyeth did not somehow “waive[],” AZBr.45, its written-description argument or overlook the court’s minimal written-description discussion. Wyeth amply addressed it, pointing to the specification and record. WBr.43-53, 57-58.<sup>4</sup>

AstraZeneca’s remaining unit-dosage written-description arguments (which again repeat enablement arguments) are fact-bound, and the jury had ample evidence to reject them. The patents expressly state: “*The 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) (emphasis added). And they continue: “[I]n general, satisfactory results are obtained” at, “preferably,” 2-500 mg. Appx207 (8:59-66). This disclosure—that the POSA (highly experienced and working with a “multi-disciplinary team” including “cancer treating clinicians,” Appx17357 (177:24-178:16)), knows how to dose—is presumed accurate. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). True, patent challengers might overcome the presumption of accuracy by giving “reason to doubt the objective truth” of the patent’s statements. *Id.* (cleaned up). But the jury could easily find AstraZeneca failed to do this. And, with respect to AstraZeneca’s ultimate burden,

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<sup>4</sup> Moreover, Wyeth’s written-description argument expressly cited back to the disclosure and Dr. Hausheer’s testimony addressing IC<sub>50</sub> values. WBr.57-58. That testimony refutes the supposedly overlooked “determination.”

the jury could easily find AstraZeneca failed to establish lack of written description by clear and convincing evidence.

As the jury heard, the patents reference a “very standard” skill in the field. Appx17548 (940:1-2) (Hausheer). Dr. Hausheer walked through the written description of unit dosage and explained the guidance provided by the patents’ stated ranges, including the patents’ comparison to reversible-inhibitor dosages, and their relationship to ranges suggested by referenced irreversible inhibitor testing (including by co-inventor Dr. Rabindran). Appx17519-20 (824:6-830:5). The court properly allowed the jury to credit that disclosure. Appx55.

Further, irreversible inhibitors were a well-known and well-tolerated class of compounds. WBr.10-12. Dr. Hausheer highlighted the patents’ disclosures of contemporaneous literature, familiar to the skilled artisan, showing that irreversible inhibitors were tolerated by humans and animals in the patents’ disclosed ranges. *E.g.*, Appx17519-20 (825:20-830:5) (“So if we work with animals ... we can definitely see what the unit dose range is.”). AstraZeneca’s Dr. Jänne agreed that prior art cited in the patents “discloses information about other irreversible inhibitors ... and their administration in daily unit doses of 2 to 500 milligrams.” Appx17475 (649:11-17). Dr. Jänne also acknowledged he had successfully determined “multiple” unit doses of an irreversible inhibitor within the claims.

Appx17477 (656:11-657:16). AstraZeneca provided no reason for the jury to disbelieve the patents' statements or require more.

AstraZeneca can suggest otherwise only by repeatedly reading disputed aspects of the record in its favor. It views the patents' *in vitro* studies and disclosures as "unrelated" to treating patients, recasts testimony at will (Drs. Hausheer and Haber), and repeats its strained reading of Godin-Heymann. AZBr.45-48, 50. Just as for enablement, AstraZeneca is not entitled to substitute its interpretation of the evidence for the jury's. *See supra* Part I.B.

AstraZeneca's argument that the patents' statement that the skilled artisan is aware of an effective unit dosage for each individual patient, Appx207 (8:57-59), somehow "contradicts" the relevance of the patents' *in vitro* data fares no better. *See* AZBr.48-49. There is nothing contradictory about highlighting the "excellent correlation" between clinical response and lab experiments, Appx211 (15:54-59), or the referenced human and animal data from other disease contexts showing an "acceptable ... safety profile," WBr.11-12, and acknowledging that the artisan would consider patients' individual circumstances, Appx207 (8:57-59).

As for the patents' IC<sub>50</sub> information, AstraZeneca resorts to an improper legal standard, arguing that IC<sub>50</sub> information, *by itself*, does not "show possession." AZBr.46-48; *see* AZBr.51. It doesn't need to. Together with the other evidence discussed above, the IC<sub>50</sub> information—including the skilled artisan's understanding

of it, Appx17520 (828:7-829:1)—rebutts AstraZeneca’s theory that therapeutically effective doses cannot be tolerated.

## II. THE CLAIMS IMPOSE NO “TOXICITY” LIMITATION

Apart from the evidentiary shortcomings of AstraZeneca’s unit-dosage arguments just discussed, those arguments rest on a premise—that the claims include a “toxicity” limitation—that contravenes settled precedent. WBr.30-36. AstraZeneca does not dispute that, without a “toxicity” limitation, its unit-dosage arguments fail.

At the outset, AstraZeneca concedes “the specification need not enable a ‘unit dosage’ with particular safety or efficacy requirements” ““that is acceptable in terms of lacking side effects,” ““meeting the FDA’s safety criteria,”” or satisfying ““any other criteria that might make a drug an attractive option for a practicing clinician.”” AZBr.28 (quoting Appx57) (emphasis omitted). That forecloses AstraZeneca’s asserted “ordinary meaning” that “the dosage cannot be unduly toxic to the patient.” AZBr.28. A demand that a dosage not be “unduly toxic” is the exact sort of “safety ... requirement[],” ““safety criteria,”” or other ““criteria ... for a practicing clinician”” that AstraZeneca disclaims.<sup>5</sup>

Precedent demonstrates why AstraZeneca’s concession is correct and indeed

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<sup>5</sup> AstraZeneca elsewhere concedes clinical testing is not a “prerequisite to patentability” unless clinical efficacy is ““expressly claim[ed].”” AZBr.51.

compelled. In *United Therapeutics Corp. v. Liquidia Technologies, Inc.*, this Court explained that claiming a method of administering “a therapeutically effective single event dose” of a pulmonary hypertension treatment “*to a human*” “does not import any additional efficacy limitations or safety limitations.” 74 F.4th 1360, 1364, 1368-69 (Fed. Cir. 2023) (quotation marks omitted) (emphasis added). The “plain and ordinary meaning” of this language required “an improvement in a patient’s hemodynamics,” and the Court declined to “insert the FDA’s responsibilities into claims” unless they “recite[d] such limitations.” *Id.* at 1369 (quotation marks omitted). In other words, the term “human” (or patient) imposes no anti-toxicity requirement. *Id.*; see, e.g., *In re Brana*, 51 F.3d at 1568; WBr.35-36. Where, as here, “the specification is silent as to whether the claimed pharmaceutical composition is limited to being nontoxic, there is no basis to import such a limitation into the claim.” *Mayne Pharma*, 927 F.3d at 1241.

AstraZeneca’s minimal attempts to distinguish *United Therapeutics* fail. First, while those claims involved a “single treatment session,” AZBr.30-31, AstraZeneca offers no reason—nor is any apparent—why toxicity standards or clinical goals would automatically apply to claims for “daily” treatment but not a “single” treatment. Second, AstraZeneca invokes the court’s speculation that there are some “inhibitors for which no dose may be found,” AZBr.31, but that merely

assumes a toxicity limitation exists in the first place (and besides, the statement lacks record support, WBr.38-53).<sup>6</sup>

If that weren't enough, AstraZeneca's demand for *in vivo* working examples, AZBr.31-32, 34-37, similarly contravenes precedent. A "patent need not contain a working example" if the POSA "will be able to practice it without an undue amount of experimentation." *Edwards Lifesciences AG v. CoreValve, Inc.*, 699 F.3d 1305, 1309 (Fed. Cir. 2012) (cleaned up); accord *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012) ("the written description requirement does not demand either examples or an actual reduction to practice" (cleaned up)). Thus, for treatment claims, "it has long been recognized that when experimentation on human subjects is inappropriate, *as in the testing and development of drugs and medical devices*, the enablement requirement may be met by animal tests or *in vitro* data." *Edwards Lifesciences*, 699 F.3d at 1309 (emphasis added); see also *United Therapeutics*, 74 F.4th at 1369 ("Title 35 does not demand that such human testing occur within the confines of [PTO] proceedings." (cleaned up)).

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<sup>6</sup> To the extent AstraZeneca suggests (without citation) that some inhibitors might not "inhibit[] EGFR and kill[] cancer cells," AZBr.31, the court correctly said otherwise. Appx58 ("AstraZeneca did not provide clear and convincing evidence that 'the claimed irreversible inhibitors do not achieve ... inhibiting EGFR and killing cancer cells.'").

AstraZeneca’s assertion that “Wyeth points to no record evidence” contradicting AstraZeneca’s proposed “ordinary meaning” gets it backwards. AZBr.28. As Wyeth showed, the specification uniformly discusses the claimed treatments without reference to safety/toxicity. Instead, it focuses on “inhibiting EGFR.” See WBr.31-32. Moreover, the claims nowhere “include the words ‘effective amount’ or ‘therapeutically beneficial.’” Appx2425. Nor do they contain language like in *Celgene Corp. v. Peter*, reciting “a method for delivering a drug to a patient ..., while avoiding the occurrence of an adverse side effect.” 931 F.3d 1342, 1347 (Fed. Cir. 2019) (emphasis added). It is AstraZeneca’s construction, not Wyeth’s, that lacks specification and claim support.<sup>7</sup>

AstraZeneca’s assertion that Wyeth improperly “seek[s] further construction” is similarly confused. AZBr.27; AZBr.42 n.10. The “unit dosage” construction that Wyeth won—i.e., the “specification’s definition” of “‘calculated to produce the desired therapeutic effect,’” Appx2436; Appx142-43—flowed directly from the court’s rejection of a “safety” limitation, Appx2436-37; Appx2424-26. AstraZeneca cannot end-run its loss by backdooring a toxicity limitation into the specification’s definition. Its unexplained appeal to “ordinary meaning,” AZBr.28, entirely ignores

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<sup>7</sup> The preambles specify the purpose for which the invention must be practiced, Appx2424-26; they impose no safety/toxicity limitation. *Contra* AZBr.42-43.

the context the specification provides and leaves Wyeth's textual arguments as to the definition's plain meaning unrebutted, WBr.31-33.

Rather than addressing the patents or conducting an actual claim-construction analysis, AstraZeneca relies on its own twist of Dr. Hausheer's testimony. He responded to the question "[w]hen you calculate a unit dose, do you make sure that dose is not so high it's going to be toxic to the patient?" by answering, "Yeah, you have several unit doses that you're going to use," and agreed that "you'll want to avoid administering a toxic dose in order to achieve the desired therapeutic effect." AZBr.26, 29 (discussing Appx17548 (939:24-940:15)); Appx57. That testimony could not alter the safety-agnostic construction the court had already given. And in context, it referred to doctors' unremarkable preference for minimizing side effects when possible, WBr.44-45, and to FDA requirements for drug approvals, Appx17548 (941:9-12) ("But by law you have to do a Phase 1 trial")—requirements not claimed (as AstraZeneca nowhere disputes).

Besides, AstraZeneca ignores Dr. Hausheer's unequivocal testimony that the sole focus of the claims' "desired therapeutic effect" is "not anything else" besides "kill[ing] cancer cells" by "interference with the EGFR pathway." Appx17519 (823:22-824:5); *accord* Appx17548 (939:9-16) ("therapeutic effect in a patient" means "the irreversible inhibition of EGFR"). AstraZeneca similarly ignores Dr. Jorgensen's testimony explaining that "[m]aking a drug that's approved by FDA,

that’s a different thing, but that’s not what the patent’s about.” Appx17559-60 (983:5-6, 984:12-985:1, 987:19-23).

Finally, the prosecution statements AstraZeneca invokes are unpersuasive. AZBr.29-30. The inventors did not distinguish Agus based on toxicity. Agus teaches treatment of *any* drug-resistant cancer by administering higher quantities of *any* TKI—not, as claimed here, treatment of gefitinib-resistant NSCLC using an irreversible inhibitor. Appx37076-77 (“Agus is solely focused on overwhelming a patient’s resistance by *overdosing with any TKI*.”); Appx17543-44 (921:23-923:23) (Hausheer) (Agus involves “any EGFR inhibitor ... in a really high dose”; “there’s no T790M. You just treat any type of tumor ...”). So the inventors noted Agus’s distinct approach of intermittent “overdosing,” thereby “*teach[ing] away* from conventional TKI therapy involving standard daily dosing” as claimed. Appx37415. Simply put, Agus teaches greatly increasing a dose (including for compounds and diseases outside the claims) administered with less frequency, whereas the patents-in-suit teach treating gefitinib resistance using irreversible inhibitors at conventional doses and intervals. Appx37413-17. That discussion nowhere suggests a toxicity limitation.

In short, this Court’s precedent, intrinsic evidence, and even extrinsic evidence like trial testimony all compel the same conclusion: no toxicity limitation.

### III. POST-VERDICT RECONSTRUCTIONS CANNOT SUPPORT JMOL

Even if the claims contained a “lethality,” “toxicity,” or other safety limitation, the procedural error of introducing it post-verdict is another reason JMOL cannot stand. WBr.53-57. While the current record shows the patents teach effective dosing notwithstanding side effects, *see supra* Part I.B, with timely notice Wyeth could have demonstrated this even more robustly. WBr.56-57. For instance, Wyeth could have developed evidence about data underlying FDA’s approval of HKI-272 to treat breast cancer. *See Nerlynx Label*, at 1, 14.<sup>8</sup>

AstraZeneca never disputes that post-verdict reconstruction is impermissible and prejudicial here. It insists only that “[t]he court did not change its construction post-verdict.” AZBr.42. AstraZeneca is wrong. Before and during trial, the court made clear that toxicity/safety standards are not part of the claims by rejecting AstraZeneca’s argument that “the patent requires this to be safe and efficacious or effective.” Appx17315-16 (12:22-13:1); *see also* Appx1127-29. Indeed, AstraZeneca affirmatively accepts that “the specification need not enable a ‘unit dosage’ with particular safety or efficacy requirements” “that is acceptable in terms of lacking side effects,” “meeting the FDA’s safety criteria,” or satisfying “any other

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<sup>8</sup> [www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208051s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf) (last accessed June 3, 2025); Appx17438 (501:6-7) (“neratinib” is HKI-272).

criteria that might make a drug an attractive option.” AZBr.28 (cleaned up). Yet AstraZeneca defends JMOL by arguing for just that—toxicity/safety requirements.

In sum, because the court’s and AstraZeneca’s unit-dosage-based reasons for JMOL turn on a construction different from the one under which the case was tried, Wyeth is entitled to reversal or, at minimum, the chance to litigate the case with notice of the governing construction.

#### **IV. THE JURY AND DISTRICT COURT CORRECTLY REJECTED ASTRAZENECA’S ALTERNATE ARGUMENTS**

AstraZeneca alternatively argues the claims are too broad to be adequately enabled or described. AZBr.53-61. These are fact-bound arguments the district court (correctly, repeatedly) held the jury was entitled to reject. Appx48-52; Appx80-88.<sup>9</sup>

*Enablement.* AstraZeneca tries to frame this case as one where “the only reasonable conclusion” is that the scope of covered compounds is “enormous,” creating an “onerous and unpredictable task.” AZBr.53-54. The record on these issues, however, was hardly “undisputed.”

Dr. Jorgensen—a preeminent expert in medicinal chemistry, drug discovery, and molecular modeling, Appx17551 (952:1-954:9)—dispelled any notion that the

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<sup>9</sup> AstraZeneca’s amici nowhere defend the district court’s basis for JMOL or AstraZeneca’s unit-dosage arguments, instead parroting AstraZeneca’s one-sided, fact-bound alternative arguments. AmicusBr.4-17.

scope was hopelessly “enormous.” He explained that the well-qualified artisan, *see* WBr.9-10 n.4, would use the known technology the specification summarized, making it a “slam dunk, no problem” to identify compounds for practicing the claims. Appx17558-59 (982:16-983:12). Among other things, the artisan knew of Stamos, cited in the patents. Appx17465 (603:20-604:4). That paper and associated data described the single x-ray crystallographic structure of EGFR bound to erlotinib—which gave precise, three-dimensional specifications about the target receptor site in cysteine 773, and thus about the shape and size necessary for irreversible inhibitors to covalently bind there. Appx20302-08 (Stamos); Appx15446, Appx15448-50; Appx17554-55 (963:4-968:17), Appx17557 (977:5-978:23); *see also, e.g.*, Appx193 (Figure 2B), Appx204 (2:61-64), Appx206 (5:17-20), Appx210 (13:45, 13:50-58). AstraZeneca used Stamos in its own work, *e.g.*, Appx40094, Appx40017; Appx17416 (413:4-414:10) (Ward), and Dr. Reider acknowledged the Stamos structure as a “bedrock” and a “very, very important feature of drug discovery,” Appx17464 (605:23-606:16).

As Dr. Jorgensen further explained, this “magnificent,” “very empower[ing] ... Stamos crystal structure” enables “straightforward” identification of existing appropriate inhibitors or design of others—“a competent POSA would be able easily to design irreversible inhibitors of EGFR” using it; “an undergraduate” could do so. Appx17553-54 (962:9-963:3); Appx17555 (967:12-968:11);

Appx17558-59 (981:4-983:12); *see also* Appx17552-55 (956:4-11, 957:1-17, 963:4-967:11), Appx17555-59 (969:10-976:4, 976:16-981:3, 984:12-986:9); Appx17464 (603:24-604:4) (Reider); Appx17388 (301:23-302:13) (Haber). AstraZeneca is thus wrong to claim that Dr. Jorgensen was “conclusory,” failed to address the “full scope,” did not “explain how” the patents narrow the scope of possible compounds (including with a “structure-function relationship”), and did not identify “disclosure in the specification identifying” “useful structures.” *E.g.*, AZBr.18, 55-57.

Rather than address this testimony from Dr. Jorgensen and other evidence refuting an “enormous” scope, AstraZeneca attempts to distract with irrelevant evidence and inconsequential arguments—none of which the jury had to accept.

**First**, AstraZeneca emphasizes its cross-examination of Dr. Jorgensen about his report in another case. AZBr.53. That report discussed the ’008 patent, which was filed almost a *decade* before the patents-in-suit, predates Stamos, and was itself far broader than the patents-in-suit, because “virtually all” of its scope “wouldn’t inhibit any kinase,” whereas the claims here “very much restrict[] the substituents” in that way. Appx17561 (992:25-994:21); Appx40785. That report thus addressed different facts, issues, and time. That is why, as Dr. Jorgensen made clear, whatever the breadth of the ’008 patent’s disclosure, the patents-in-suit encompassed and taught a “universe of possible compounds ... not in the billions, but rather far smaller”; the artisan “would understand” it was “limited by certain features ... to

covalently bind to cysteine 773.” Appx49-50 (citing Appx17553 (962:9), Appx17557-58 (977:5-21, 979:11-25, 980:20-24), Appx17561 (993:22-994:3)).

**Second**, AstraZeneca grabs a statement from prosecution—“the highly unpredictable nature of the art,” Appx36977—but ignores context and countervailing evidence. AZBr.54-55. The prior art in question—Agus—was, as noted above, far broader, teaching “overdosing” using any of a “laundry list of TKI’s” well beyond irreversible inhibitors, and not focusing on “the specific selections of disease and TKI” of the patents-in-suit. Appx36975-77 (Agus’s compounds “even include[] ... an antibody,” which is “not ... a TKI”); *see supra* p. 20. It was in that distinct context (and before the patents-in-suit) that unpredictability existed.

**Third**, AstraZeneca asserts the narrow theory that the specification’s three example compounds are insufficient because they are not representative of a single other (Tagrisso). AZBr.18, 54. The district court correctly recognized this was a jury question: “Wyeth’s expert testified that Tagrisso ... did not have meaningfully different structural features compared to the example compounds and structures disclosed in the specification” and “[t]he jury was not obligated to credit AstraZeneca’s evidence over Wyeth’s.” Appx65. As Dr. Jorgensen explained, Tagrisso bears the salient, representative features, its differences were “no big deal,” and AstraZeneca’s suggested distinctions were “exaggeration[s],” “attempts to confuse,” and “misleading to the uninitiated.” Appx17558 (979:2-980:24)

(discussing each salient feature and explaining why “medicinal chemists would look at these structures and see the similarities, the core, the heteroaryl group or the aryl and the acrylamide, and there’s no big difference here at all. Same intellectual entities”).

Cross-examination of AstraZeneca witnesses likewise exposed these “distinctions” as overstated. Appx17463-64 (601:20-603:4); Appx17422 (437:2-25). For instance, AstraZeneca erroneously asserts it is “undisputed” that Tagrisso was uniquely designed to target mutant EGFR while the patents-in-suit “taught the wrong solution” of “targeting wild-type EGFR.” AZBr.1-2, 7, 9, 59-60. But Drs. Reider and Ward both admitted that Tagrisso also acts on wild-type EGFR and that Tagrisso causes side effects associated with wild-type inhibition. Appx17423 (439:6-442:8); Appx17477 (658:11-21); *see also* Appx17552-53 (957:18-961:9) (Jorgensen: Q: “[Dr. Reider’s] taken the position that ... the only thing that Dr. Haber and the other inventors actually taught in the patent was how to attack the wild type, the healthy EGFR. Do you agree with that?” A: “No, I don’t understand that. The assays were done with cells that have the T790M mutation.”); Appx17518 (821:16-822:6) (Hausheer: claims target “sensitizing mutations,” “not ... wild type” EGFR). As the court recognized, “that Tagrisso ... [is] particularly effective does not mean that it

does not share the basic features of the so-called second-generation irreversible EGFR inhibitors disclosed in the patents-in-suit.” Appx65-66.<sup>10</sup>

For similar reasons, AstraZeneca’s claim that “Wyeth’s experts admitted that Tagrisso’s structure is not taught by the specification,” AZBr.54, is highly misleading. One of its citations is to its *own* expert, not Wyeth’s. Appx17479 (663:4-14) (Jänne). The other, from co-inventor Dr. Haber, does not support AstraZeneca. Appx17396 (333:5-7); *accord* AZBr.58, 60 (invoking similar testimony at Appx15129-30 for written description). Additionally, Dr. Haber is “not a chemist” and does not design drugs. Appx17395-96 (329:20-330:5, 333:5-7). The skilled artisan, though, *would* have “at least three years of practical experience in drug discovery and development” and work with “team members with experience developing cancer treatments, including ... medicinal chemists.” Appx17357 (177:25-178:16); *cf.* Appx15145 (110:02-06) (noting co-inventor Dr. Rabindran’s “decades studying development compounds”). And, Dr. Jorgensen, an expert chemist the jury was entitled to credit, explained that the specification taught, and the artisan knew about, irreversible inhibitors that, like Tagrisso, use a single-ring

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<sup>10</sup> AstraZeneca makes similar written-description arguments, citing Dr. Kwak and a post-priority article. AZBr.57, 59-60. Both discuss only relative potency; neither establishes that the patents do not show possession of Tagrisso for practicing the claims. Appx15141 (180:18-181:6) (Kwak discussing Appx39657); Appx39674.

structure. *E.g.*, Appx17558 (980:3-24) (“Tagrisso has another very common kinase core”); Appx17559 (985:16-19) (“Did [the patents] disclose that single-ring kinase inhibitor, imatinib?” A. “Yes, that’s mentioned. And as I said, every POSA is thinking about common kinase cores.”). Nor is Dr. Haber a lawyer; he was not testifying about the doctrine of representative examples. He was simply acknowledging the unremarkable and undisputed point that these are method-of-treatment claims, *see* Appx17396 (332:23-333:4), *i.e.*, they do “not claim compounds,” Appx17463 (601:6-17) (Reider).

Nor did the examiner’s view that the specification does not teach Tagrisso’s structure bind the jury. *See* AZBr.54. To start, the clear and convincing evidence standard is inapplicable to examination: Even “on the same evidence,” the PTO and juries can “quite correctly come to different conclusions.” *Stryker Corp. v. Zimmer, Inc.*, 837 F.3d 1268, 1278 (Fed. Cir. 2016) (cleaned up). And the jury here (unlike the examiner) benefited from an extensive record with copious expert testimony. Moreover, the jury heard “several reasons” examiners might err. Appx17338; FJC Video at 14:15-15:00.<sup>11</sup> Once again, the jury did not have to agree that Tagrisso differs because the patents-in-suit “target wild-type [*i.e.*, unmutated, healthy] EGFR.” *E.g.*, AZBr.59. As Dr. Jorgensen explained, the patents use “standard language”

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<sup>11</sup> <https://www.youtube.com/watch?v=ax7QHQTbKQE> (last accessed June 3, 2025).

from which the artisan would understand they target mutated, cancerous cells. Appx17553 (960:17-962:4); *see also supra* pp. 25-27.

**Fourth**, while AstraZeneca suggests that the specification’s statement about “larger compound[s],” Appx210 (13:3-13), prevented POSAs from understanding the claims’ limited scope, AZBr.55, the court correctly understood that “Wyeth presented evidence, which the jury was entitled to credit, that a POSA would not be misled by this statement because a POSA would know that large compounds cannot covalently bind to cysteine 773 of EGFR” as the claims require. Appx51-52. As Dr. Jorgensen explained, small molecules are needed because that’s what can “get inside the cell” to bind. Appx17557-58 (978:9-979:1).<sup>12</sup>

**Finally**, AstraZeneca’s argument about the inventors’ supposed “failure” to identify an inhibitor “functioning as required,” AZBr.56-57, repeats the error of its unit-dosage arguments by assuming a toxicity requirement that is not claimed and that in any event was met. *See supra* Parts I-II.

**Written Description.** AstraZeneca’s written-description argument mostly repeats its enablement argument—likewise and incorrectly premised on a “vast functional genus,” overstated distinctions between Tagrisso and the patents’ example inhibitors, and the supposed inadequacy of *in vitro* disclosure. AZBr.57-

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<sup>12</sup> The three example compounds are indisputably all small molecules. Appx17493 (719:3-8) (Reider).

61. “The jury was not obligated to credit AstraZeneca’s evidence over Wyeth’s.” Appx65. Dr. Jorgensen explained that the specification as understood by the skilled artisan discloses the claims. *See supra* pp. 22-24, 26-29. And contrary to AstraZeneca’s contention, he also plainly “connected” the specification’s disclosure “to the full scope of” inhibitors used in the claims, including by way of the example classes and compounds, and he “provide[d] evidence that function can be predicted by structure.” AZBr.59-60; *see supra* pp. 22-29; *see also* Appx17555-57 (970:23:1-978:4).

All that remains is AstraZeneca’s argument that Dr. Jorgensen’s testimony “misses the point of” showing possession “*from the specification.*” AZBr.58. AstraZeneca drastically overstates the point. As the jury was instructed, the written-description analysis accounts for “the existing knowledge in the relevant field.” Appx149. What matters “is the disclosure in the patent” *and* “evidence outside” demonstrating what the skilled artisan “would have known as of the pertinent date.” *In re Xencor, Inc.*, 130 F.4th 1350, 1362 (Fed. Cir. 2025). And here, the skilled artisan’s level of knowledge is “high,” and the patents-in-suit explicitly reference the prior knowledge. Appx17552 (955:4-8); *supra* pp. 22-24, 27-28. Even an undergraduate could predictably identify inhibitors to practice the claims—based on the specification’s guidance and the patents’ Stamos citation. *Supra* pp. 22-24. AstraZeneca’s case, *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d

1336 (Fed. Cir. 2013), neither upended this law nor presented analogous facts. The specification in *Novozymes*—unlike here—“nowhere describe[d]” any claim “as an integrated whole” nor even “any ‘blaze marks’” to distinguish “among a slew of competing possibilities,” and the patentee’s expert essentially “admitted that her testimony suffered from” legal flaws. *Id.* at 1349. Similarly, in *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997), it was “undisputed” that a claimed feature was undisclosed in the relevant intervening application, whereas here, Tagrisso’s supposed distinctions are illusory or unimportant. Appx17558 (979:2-980:24) (Jorgensen).

## **V. WYETH IS ENTITLED TO PURSUE PRE-ISSUANCE DAMAGES**

AstraZeneca’s two arguments against pre-issuance damages fail.

1. AstraZeneca first insists 35 U.S.C. § 154(d) protects inventors against only direct infringement. AZBr.61-63. But as AstraZeneca itself observes, statutes are presumed “‘harmonious with existing law and judicial concepts.’” AZBr.62-63. That presumption shows that § 154(d) bars *all* pre-issuance infringement, including knowing inducement. WBr.58-64.

Congress enacted § 154(d) together with § 122(b)—a new publication requirement that created a risk of free-riding off pending applications. Accordingly, § 154(d) “enables [inventors] to collect a reasonable royalty for infringement that occurs during the time the application is published.” S. Rep. No. 105-42, at 51

(1997). Section 154(d) is presumed harmonious with § 271(b)'s pre-existing command that an inducer “shall be liable as an infringer,” and does not somehow allow unfair exploitation by “all manner of actors, including inducers,” as AstraZeneca would have it, AZBr.62. Moreover, § 154(d)'s language parallels § 154(a)'s prohibition on post-issuance infringement. Neither provision expressly mentions induced infringement. But nobody doubts that § 154(a) protects against induced infringement post-issuance. Section 154(d) does likewise pre-issuance.

AstraZeneca invokes *National Presto Industries, Inc. v. West Brand Co.*, 76 F.3d 1185 (Fed. Cir. 1996), a *pre*-§ 154(d) case. At the time, patent rights began when “the patent issues,” § 154(a)(2), so damages for any type of infringement were limited to post-issuance. *National Presto*'s holding that induced infringement does “not reach actions taken before issuance,” 76 F.3d at 1194-96, is necessarily limited to that context when direct infringement was likewise limited. Enactment of provisional rights changed the premise on which *National Presto* rested. See *In re Forest*, 134 F.4th 1198, 1202-04 (Fed. Cir. 2025) (provisional rights are “placeholder rights” “preced[ing]” issued-patent rights).

2. AstraZeneca next argues that publicly available amendments are not part of an earlier-published application under § 154(d). AZBr.63-64. The district court did not reach this argument. This Court should reject it.

Section 154(d) grants provisional rights as of “the date of *publication* of the *application* for such patent under section 122(b)” if certain conditions are met, such as “actual notice of *the published patent application*” and issued claims “substantially identical” to claims “in the *published patent application*.” § 154(d)(1)-(2) (emphasis added). The relevant terms (italicized) take their ordinary meaning.<sup>13</sup> *Mohamad v. Palestinian Auth.*, 566 U.S. 449, 454 (2012). A “patent application” is “[a]n inventor’s request for a patent,” which can have “amendment[s].” *Patent Application & Patent-Application Amendment*, BLACK’S LAW DICTIONARY 1158-1159 (8th ed. 2004) (“BLACK’S”); *see also* Appx8635 (only 11.4% of applications allowed without amendment). And “publication” means “distribution of” the application “to the public.” BLACK’S 1264. So when patent applications, as amended, are “distribut[ed]” to the public, they are “published,” as amended. AstraZeneca’s reading—attributing to Congress an intent to protect inventors differently based on the happenstance of whether their claims were amended during prosecution—contradicts the plain meaning and the well-established fact that applications are routinely amended, not frozen in time. Nor would this make pre-issuance damages “the rule,” *see* AZBr.64, given § 154(d)’s other stringent limitations (like “actual notice” and “substantially identical”).

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<sup>13</sup> The Court owes no deference to regulatory definitions. *Loper Bright Enters. v. Raimondo*, 603 U.S. 369, 412 (2024); *contra* AZBr.63.

Here, the relevant applications were “published” August 14 (’314 patent) and October 28, 2019 (’162 patent), when the amendments were electronically filed.<sup>14</sup> Appx8913-16; *see, e.g.*, Appx37409-10; Appx37422-24. Wyeth is entitled to pursue pre-issuance damages as of then.

### CONCLUSION

JMOL should be reversed and the case remanded for further proceedings on relief for AstraZeneca’s infringement.

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<sup>14</sup> AstraZeneca’s view that “[t]here is no dispute that the asserted claims are *not* substantially identical to Wyeth’s published claims,” AZBr.63, (1) depends on AstraZeneca’s incorrect premise that Wyeth’s amended claims were not “published,” and (2) ignores evidence that the asserted claims are “substantially identical” to Wyeth’s amended claims. Appx8912-16 (Weiss).

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## CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) and Federal Circuit Rule 32(b)(1) because it contains 6,994 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).
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