United States Court of Appeals for the Federal Circuit

WYETH LLC,
Plaintiff-Appellant

v.

ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA AB,
Defendants-Appellees

2024-2325

Appeal from the United States District Court for the District of Delaware in No. 1:21-cv-01338-MFK, Judge Matthew F. Kennelly.

Decided: July 9, 2026

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KEANE, EINAR STOLE, ALEXANDER TRZECIAK, ASHLEY MARIE WINKLER.

Before LOURIE, LINN, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Wyeth appeals from a final decision of the United States District Court for the District of Delaware granting judgment as a matter of law ("JMOL") of invalidity of asserted claims 1, 3, and 9 of U.S. Patent 10,603,314 ("the '314 patent") and asserted claim 1 of U.S. Patent 10,596,162 ("the '162 patent") (together, "the asserted patents"). *Wyeth LLC v. Astrazeneca Pharms. LP*, No. 21-CV-1338, 2024 WL 3823006 (D. Del. Aug. 14, 2024) ("*Decision*"). For the following reasons, we affirm.

BACKGROUND

Wyeth's '314 and '162 patents generally relate to methods of cancer treatment. Specifically, the asserted patents claim methods of using irreversible inhibitors to treat "gefitinib and/or erlotinib resistant" non-small cell lung cancer ("NSCLC"). '314 patent, Abstract. NSCLC is associated with overactivity of the epidermal growth factor receptor ("EGFR"), a receptor tyrosine kinase that regulates cell growth and division. *Id.* at col. 2 ll. 1–3. Drugs used to treat NSCLC—known as EGFR tyrosine kinase inhibitors ("TKIs")—bind to specific regions of EGFR and inhibit signaling that would otherwise promote cancer cell growth. *Id.* at col. 2 ll. 52–62.

Two TKIs, gefitinib and erlotinib (together, "g/e"), showed promise in treating NSCLC. Gefitinib and erlotinib are "reversible" inhibitors, meaning they form non-covalent bonds with EGFR that dissociate over time. As a result, "[a] significant limitation in using [reversible inhibitors such as g/e] is that recipients thereof may develop a resistance to their therapeutic effects after they initially

respond to therapy, or they may not respond to EGFR-TKIs to any measurable degree at all." *Id.* at col 3 ll. 19–23; *see also id.* at col. 7 ll. 57–63. The inventions of the asserted patents seek to address this shortcoming through the use of "irreversible" EGFR inhibitors. That is, the asserted patents claim a method for treating "g/e resistant NSCLC" by using "irreversible" EGFR inhibitors that covalently bind to a specific amino acid at a specific location of EGFR. *Id.* at col. 3 ll. 43–49, col. 7 ll. 15–19. Specifically, exemplary claim 1 of the '314 patent recites:

> 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.

Id. at col. 35 ll. 52–60 (emphases added).

The specification discloses that the claimed "irreversible EGFR inhibitor may be any compound which binds to cysteine 773 of EGFR (SEQ ID NO: 1)."[1] *Id.* at col. 3 ll. 57–59. It then describes, in total, three compounds (*i.e.*, EKB-569, HKl-357, and HKl-272) as examples of such EGFR inhibitors. *Id.* at col. 13 ll. 50–51. In describing the *in vitro* experimentation involving these three compounds, the specification states that the results "demonstrate[d] increased killing of NSCLC cells harboring an EGFR mutation." *Id.* at col. 16 ll. 21–22.

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[1] The '314 and '162 patents' specifications are materially the same, and we therefore cite the '314 specification as exemplary.

The specification also discloses that "[t]he therapeutic compositions of this invention, e.g. irreversible EGFR inhibitors, are conventionally administered intravenously, as by injection of a unit dose, for example." *Id.* at col. 9 ll. 30–32. It further states that the claimed "unit dosage" refers to "physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material *calculated* to produce the desired *therapeutic effect* in association with the required diluents; i.e., carrier, or vehicle." *Id.* at col. 9 ll. 33–38 (emphases added). As it relates to the claimed requirements of "administering [a unit dosage] daily to the patient," *id.* at col. 35 ll. 52–60, the specification explains that calculating a unit dosage to achieve such therapeutic effect in a patient "depends on the subject to be treated, capacity of the subject's system to utilize the active ingredient, and degree of therapeutic effect desired," *id.* at col. 9 ll. 42–46, in addition to "the particular compound employed, the mode of administration and the severity of the condition being treated," *id.* at col. 8 ll. 55–57.

Accounting for those variable factors, the specification states that the "[p]recise amounts of active ingredient . . . depend on the judgment of the practitioner and are peculiar to each individual." *Id.* at col. 9 ll. 44–46. In terms of any additional guidance, the specification explains that a "skilled artisan is aware of the effective dose for each patient," *id.* at col. 8 ll. 57–58, and offering that, "in *general*, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of body weight," and that the "total daily dosage is *projected* to be from about 1 to 1000 mg, preferably from about 2 to 500 mg," *id.* at col. 8 ll. 59–66 (emphases added).

In September 2021, Wyeth filed a complaint in the district court asserting that AstraZeneca induced infringement of the '314 and '162 patents based on marketing, distribution, and sales of its irreversible EGFR inhibitor

Tagrisso (osimertinib). *Decision*, 2024 WL 3823006, at *2. The district court construed several terms, including the term "unit dosage." *See Puma Biotechnology, Inc. v. Astrazeneca Pharms. LP*, No. 21-CV-1338, 2023 WL 2683559, at *9 (D. Del. Mar. 29, 2023) ("*Claim Construction Decision*"). The court explained that the "claimed methods involve administering daily a 'unit dosage' of an irreversible EGFR inhibitor that covalently binds to a specific part of the enzyme." *Id.* at *1. The court identified that the specification "expressly define[d]" a "unit dos[age]," and ultimately adopted that definition: "physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material *calculated* to produce the desired *therapeutic effect* in association with the required diluents; i.e., carrier, or vehicle." *Id.* at *9 (quoting '314 patent col. 9 ll. 33–38 (emphases added)).

The case proceeded and after a five-day trial, a jury concluded that the asserted claims were not invalid and that AstraZeneca induced infringement of the asserted claims, awarding Wyeth $107,500,000 in damages. *Decision*, 2024 WL 3823006, at *3. AstraZeneca renewed its motion for JMOL post-verdict and argued, in part, that no reasonable jury could have found the asserted patents not invalid. *Id.* at *1. As relevant on appeal, AstraZeneca argued that the asserted claims were invalid for lack of enablement. *Id.* at *9. Specifically, it argued that "the patents claim but do not enable treatment via a 'unit dosage—i.e., a predetermined quantity of active material calculated to produce the desired therapeutic effect.'" *Id.* (quoting '314 patent col. 9 ll. 36–37). "In [AstraZeneca's] view, identifying the unit dosage for even just ***a single compound*** is highly unpredictable and involves [a] tremendous amount of work and experimentation." *Id.* at *12 (cleaned up). Moreover, it contended that even while the asserted patents identify "unit dosage" ranges of 1 to 1,000 mg and 2

to 500 mg, those ranges were too broad and provided insufficient guidance for a skilled artisan to determine a suitable dosage. *Id.*

Wyeth disagreed and "argue[d] that the patents provide sufficient disclosure of 'unit dosages' that would achieve the desire[d] therapeutic effect of interfering with the EGFR pathway and killing cancer cells and that determining the dosage for any given irreversible EGFR inhibitor would not require undue experimentation." *Id.* It added that AstraZeneca's arguments sought to improperly add clinical requirements of toxicity, safety, and efficacy, which fall within the domain of FDA. *Id.* at *12–13.

The district court granted JMOL of invalidity for lack of enablement of the asserted claims determining that no reasonable jury could have found the asserted claims not invalid. *Id.* at *15. At the outset of its analysis, the court made clear that the asserted claims do not require "FDA approval []or clinical effectiveness." *Id.* at *13. At the same time, it rejected Wyeth's characterization that the asserted patents merely "claim 'a method for killing cancer cells,' . . . full stop." *Id.* Rather, the district court explained that the asserted patents claim a method of treating g/e resistant NSCLC "*in a patient*" with "a unit dosage" that must be "administer[ed] daily *to the patient*." *Id.* (quoting '314 patent col. 35 ll. 53–57). In other words, it concluded that the claims do not require "ideal or optimal dos[ing]" as the FDA requires but do require "that the 'unit dosage' 'produce[s] the desired therapeutic effect' *in a patient*." *Id.* (citing *Claim Construction Decision*, 2023 WL 2683559, at *9 (emphasis added)).

The district court next turned to the evidence presented at trial. *Id.* at *13–14. It concluded that AstraZeneca presented clear and convincing evidence that no reasonable jury could have found that the asserted patents enabled a skilled artisan to administer the claimed "unit

dosage" of the claimed irreversible EGFR inhibitor to a patient without undue experimentation. *Id.* at *14. The court emphasized that (1) the specification disclosed no working examples of unit dosages administered to patients, and (2) AstraZeneca presented unrebutted evidence that some disclosed dosage levels would be toxic, including doses required to achieve a therapeutic effect in patients. *Id.*

The district court relied on trial testimony of Wyeth's own experts agreeing that a therapeutic unit dosage in a patient must avoid toxic doses, *see* J.A. 17548, and further agreeing that the specification's disclosed dosage ranges exceed the maximum tolerated dose for two of the disclosed compounds, *see* J.A. 17397–98, J.A. 17549, and potentially the third, *see* J.A. 17563. *See Decision*, 2024 WL 3823006, at *14. It also relied on testimony of the inventors of the asserted patents who explained that, via a post-application 2008 Godin-Heymann publication, the "concentrations required *in vitro* may not be achievable in patients due to drug toxicity." J.A. 11804, 11807; *see also* J.A. 17397–98 (co-inventor Dr. Haber testifying that "[t]he concentrations in the test tube are higher than those you can give to patients" and specifically agreeing that the drug concentrations in the asserted patents were found to be "five times higher" than what could be administered to patients).

In view of that evidence, the district court concluded that the asserted patents "provide[d] 'only a starting point, a direction for future research' that place[d] the burden on a [skilled artisan] to conduct 'an iterative, trial-and-error approach to practice the claimed invention.'" *Id.* at *15 (quoting *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 939–41 (Fed Cir. 2010)). It also explained that the experimentation necessary to achieve a suitable unit dosage would not be routine because the asserted patents lacked guidance on how a skilled artisan could reliably screen compounds to determine their therapeutic dosage ranges. *Id.* In sum, the district court held "the asserted claims of the '314 and '162 patents [ ] invalid for failure to meet the

enablement requirement of 35 U.S.C. § 112(a)" and granted AstraZeneca's motion for JMOL of invalidity. *Id.*

Wyeth timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Wyeth asks us to reinstate the jury verdict on the ground that the district court erred in granting JMOL of invalidity for lack of enablement of the asserted claims of the '314 and '162 patents. It contends that the district court improperly changed its construction of the term "unit dosage" post-verdict by imposing additional clinical safety and efficacy requirements. *See* Wyeth Op. Br. 24–26. It also argues that the district court further erred by testing its new and flawed construction against the jury's verdict in its enablement analysis, and that even if such construction were appropriate, its grant of JMOL of lack of enablement fails on the evidence.[2] *See id.* We disagree and discuss each argument in turn.

I

We apply our own law with respect to patent law issues. *Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356, 1359 (Fed. Cir. 1999) (en banc in relevant part). For matters not unique to patent law, we apply the law of the regional circuit, here, the Third Circuit. *Versata Software, Inc. v. Callidus Software, Inc.*, 780 F.3d 1134, 1136 (Fed. Cir. 2015) (applying Third Circuit law). The Third Circuit reviews grants and denials of motions for JMOL under Rule 50(b) *de novo*. *Cordance Corp. v. Amazon.com, Inc.*, 658 F.3d 1330, 1333 (Fed. Cir. 2011) (citing

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[2] Wyeth also appeals a second issue regarding pre-patent-issuance damages and provisional rights under 35 U.S.C. § 154(d). Because we affirm the district court's grant of JMOL of invalidity, we do not reach that issue.

Lightning Lube, Inc. v. Witco Corp., 4 F.3d 1153, 1166 (3d Cir. 1993)). Moreover, in the Third Circuit, "JMOL is proper when after 'viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find' for the nonmovant." *Id.*

A

We first address claim construction. Wyeth contends that the district court improperly imported clinical safety and efficacy requirements into the claims because, in its view, the claims require only that the "unit dosage" provide the therapeutic effect of "inhibiting EGFR and killing cancer cells" full stop. Wyeth Op. Br. 24. It argues that because the claims do not include clinical-trial endpoints, a grant of JMOL based on the importation of unclaimed safety standards, or any consideration of "a *safe* unit dosage," cannot be supported. *Id.* (citing *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1369 (Fed. Cir. 2023), *cert. denied*, 144 S. Ct. 873 (2024) ("Absent incorporation of safety and efficacy requirements in the claims," arguments "concerning the safety and efficacy of treating . . . patients [are] not before us."")). We disagree. Wyeth mischaracterizes the claims and the district court's interpretation of those claims.

"We review claim construction based on intrinsic evidence *de novo* and review any findings of fact regarding extrinsic evidence for clear error." *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 130 F.4th 1372, 1378 (Fed. Cir. 2025) (citation omitted). "Claim terms are generally given their plain and ordinary meaning, which is the meaning that one of ordinary skill in the art would ascribe to a term when read in the context of the claims, specification, and prosecution history." *Id.* at 1378–79 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313–17 (Fed. Cir. 2005)(en banc)). Ultimately, "[t]he construction that stays true to

the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1316 (citation omitted).

While Wyeth is correct that the claims do not require FDA-type clinical safety or efficacy standards, it fails to appreciate and give meaning to other relevant claim terms—namely, that the claimed "unit dosage" must be "administer[ed] daily" to a human "patient." '314 patent col. 35 ll. 53–57. Each of those terms should be afforded meaning. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so." (citations omitted)). Moreover, the district court's pre-trial construction of the term "unit dosage," which adopts the specification's definition, is unchallenged. Thus, "unit dosage" refers to "physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material *calculated* to produce the desired *therapeutic effect* in association with the required diluents; i.e., carrier, or vehicle." *Claim Construction Decision*, 2023 WL 2683559, at *9 (emphases added) (citing '314 patent col. 9 ll. 34–38).

The claims therefore plainly require the daily administration of a unit dosage *to a patient* to achieve a therapeutic effect in treating g/e-resistant NSCLC, not merely the identification of compounds capable of inhibiting EGFR activity *in vitro*. That interpretation does not import any FDA-type safety or efficacy requirements into the claims as Wyeth contends. It simply gives operative meaning to the claim language itself, which necessarily contemplates some repeatable dosing regimen calculated to produce a therapeutic effect *in a patient*. In particular, the requirement that a "unit dosage" must be "administer[ed] daily to the patient" draws the claims beyond merely requiring "killing cancer cells," yet constrains them short of requiring full-

blown FDA-type clinical safety standards. *See* '314 patent col. 35 ll. 53–57.

The specification reinforces that plain reading of the claims. Rather than describing dosage solely in terms of whether a compound can kill cancer cells or inhibit EGFR activity, the patent explains that calculating a therapeutically effective dosage "depends on the subject to be treated, capacity of the subject's system to utilize the active ingredient, and degree of therapeutic effect desired." '314 patent col. 9 ll. 42–44. The specification further recognizes that the "[p]recise amounts of active ingredient . . . depend on the judgment of the practitioner and are peculiar to each individual." *Id.* at col. 9 ll. 44–46. Together, these disclosures support the interpretation that the claimed "unit dosage" contemplates a dosage regimen tailored for practical administration to a human patient, not merely any concentration capable of producing anti-cancer effects *in vitro*.

The district court therefore did not err in its claim construction, nor its elaboration of that construction, post-verdict. In fact, the court maintained on JMOL that "there is no requirement that the asserted 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." *Decision*, 2024 WL 3823006, at *13. It also explained that the claims' lack of FDA-type limitations does not necessarily mean that the claims therefore provide no meaningful limitations on dosing. *See id.* at *13–14. Thus, the court simply reinforced its prior construction of the claims, explaining that they require the administration of a unit dosage "calculated to produce the desired therapeutic effect" *in a patient*. *See id.* at *13. That the court, in part, framed the bounds of this limitation in terms of "toxicity" concerns, *see id.* at *13–14, simply reflects a recognition that the requirement of "administering daily to the

patient" must have some operative meaning, *i.e.*, a repeatable dosing regimen in human patients. It does not mean that the claims require more particular FDA-type clinical standards of safety or efficacy.

Finally, the district court did not improperly amend its construction post-verdict, as Wyeth contends. *See* Wyeth Op. Br. 25–26. Before and after trial, the court construed the claims to require daily administration of a "unit dosage" "to produce the desired therapeutic effect" in a patient. *Compare Claim Construction Decision*, 2023 WL 2683559, at *9, *with Decision*, 2024 WL 3823006, at *13. The district court's "elaboration" on its construction of "unit dosage" post-verdict was permissible to "clarif[y] what was inherent in the construction." *Cordis Corp. v. Bos. Sci. Corp.*, 658 F.3d 1347, 1356 (Fed. Cir. 2011).

We therefore find no error in the district court's claim construction nor its elaboration of that construction on JMOL.

B

We next address enablement. Wyeth argues that the district court erred in granting JMOL because, viewing the evidence in the light most favorable to Wyeth, a reasonable jury could have concluded that AstraZeneca failed to prove by clear and convincing evidence that the asserted claims require undue experimentation to determine a non-toxic or non-fatal unit dosage for daily administration to a patient. *See* Wyeth Op. Br. 37–45. We disagree. Wyeth mischaracterizes the district court's analysis, and, regardless, the specification fails to enable the claims as properly construed.

"Enablement is a legal question based on underlying factual determinations." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 684 (Fed. Cir. 2015) (citation omitted). The enablement requirement is satisfied

when the specification contains sufficient disclosure to permit "a person of skill in the art to make and use the claimed invention." *Id.* (citing 35 U.S.C. § 112). In particular, "the specification must enable the *full scope* of the invention as defined by its claims." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023) (emphasis added). In other words, "[t]he more one claims, the more one must enable." *Id.* And while some experimentation is permissible, "the specification . . . must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1365 (Fed. Cir. 2023).(quoting *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012)).

As discussed above, the claims require administering an irreversible EGFR inhibitor daily in a functionally-defined "unit dosage"—an amount calculated to produce a therapeutic effect "in a patient." *See Claim Construction Decision*, 2023 WL 2683559, at *9 (citing '314 patent col. 9 ll. 34–38). Moreover, the specification explains that the claimed "irreversible EGFR inhibitor may be *any* compound which binds to cysteine 773 of EGFR (SEQ ID NO: 1)." *Id.* at col. 3 ll. 57–59 (emphasis added). Thus, to enable the claims, the specification must provide guidance to allow a skilled artisan to determine a daily unit dosage calculated to produce a therapeutic effect in a patient across the full scope of claimed compounds without undue experimentation. *See Baxalta*, 81 F.4th at 1365. Specifically, in the context of the asserted claims, the specification must provide some basis for translating information about the disclosed compounds' *in vitro* activity into the claimed daily dosing regimen "in a patient," *see* '314 patent col. 35 ll. 53–55, rather than leaving that determination entirely to a skilled artisan's knowledge and experimentation. *See Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1159 (Fed. Cir. 2019) ("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." (quoting *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997))).

Here, however, the specification leaves the determination of the claimed "unit dosage" entirely to the knowledge of the skilled artisan. *See* '314 patent col. 8 ll. 57–58 ("The skilled artisan is aware of the effective dose for each patient."). While the knowledge of one of ordinary skill may play an important role in enablement, it may not provide the only means to enable these specific claim limitations. *See Idenix*, 941 F.3d at 1159. That is what a specification of a patent must provide. *See id.* It is undisputed that the specification provides no working examples of any unit dosage calculated to achieve a therapeutic effect and suitable for daily administration in human patients. *See Decision*, 2024 WL 3823006, at *14. Instead, the specification identifies only three compounds as examples of preferred embodiments: EKB-569, HKl-357, and HKl-272. *Id.* at col. 3 ll. 56–57, col. 13 ll. 50–51. With respect to those compounds, the specification describes *in vitro* experimentation without any further description of (1) how to extrapolate *in vivo* dosing from those *in vitro* results or (2) any other teachings sufficient to allow a skilled artisan to calculate a "unit dosage" as claimed. Those *in vitro* data alone are insufficient to enable these claims. *See, e.g.*, *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1217 (Fed. Cir. 1991) ("[T]he district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.").

Wyeth points to the asserted patents' disclosure of prior-art studies involving various irreversible EGFR inhibitors, as well as animal studies and later clinical experience, to argue that skilled artisans would have understood that irreversible inhibitors could be administered safely and could have determined appropriate dosages without concern that patients would die. *See* Wyeth

Op. Br. 38–43. But that evidence does not answer the relevant question. The issue is not whether skilled artisans knew that some irreversible EGFR inhibitors could be administered to patients, but whether the specification teaches how to determine the claimed therapeutically effective daily "unit dosage" for the claimed compounds. *See Idenix*, 941 F.3d at 1159. The specification provides no such guidance, instead leaving dosage determination entirely to the skilled artisan, which in effect requires experimentation. *See* '314 patent col. 8 ll. 57–58.

Although the specification recites dosage ranges, *see id.* at col. 8 ll. 59–66, they are qualified as "general," *id.* at col. 8 l. 63, and "projected," *id.* at col. 8 l. 67, ranges, and the specification provides no further explanation of how those ranges were derived, how a skilled artisan would select among them for a given compound, or how they relate to the claimed unit dosage calculated to produce a therapeutic effect in a patient. The patent thus identifies ranges of "projected" daily unit dosage for administration to a patient, while leaving the skilled artisan to supply the critical teachings necessary to achieve or validate that projection. And while "a specification need not disclose what is well known in the art," that "oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *Genentech*, 108 F.3d at 1366. Thus, where, as here, the specification omits critical guidance needed to practice the claimed invention, requiring skilled artisans to fill those gaps through their own experimentation, undue experimentation is required. *See id.*

Moreover, as the trial record shows, when applying the dosage ranges disclosed to the three compounds disclosed, at least two of those compounds—HKI-272 and EKB-569––are not compatible for use in patients because they far exceed the maximum tolerated dose in humans. J.A. 17397–98; J.A. 17549. For instance, AstraZeneca presented unrebutted evidence that, for those two compounds, all therapeutically effective dosage levels, across the disclosed

dosage ranges, would exceed the maximally tolerated dose in humans. *Decision*, 2024 WL 3823006, at *14 (citing various trial testimony presented by AstraZeneca).

Indeed, not only did Wyeth fail to rebut the evidence on those issues but its own experts agreed. For instance, Wyeth's invalidity expert Dr. Hausheer agreed that when calculating a unit dosage for a patient, a skilled artisan would want to avoid toxic doses to achieve a therapeutic effect. *See* J.A. 17548. Another Wyeth witness and co-inventor Dr. Haber explained that the specification's dosage ranges far exceed the maximum tolerated dose threshold for at least one of the three compounds identified in the asserted patents (HKI-272) by a factor of more than "five." J.A. 17397–98 (testifying that "[t]he concentrations in the test tube are higher than those you can give to patients" and agreeing that the drug concentrations in the asserted patents were "five times higher" than what could be administered to patients); *see also* J.A. 11804, 11807 (inventors of the asserted patents explaining in their 2008 Godin-Heymann publication that the "concentrations required in vitro may not be achievable in patients due to drug toxicity."). Wyeth's experts further testified that the same is true for compound EKB-569, and may also be true for compound HKI-357. *See* J.A. 17549; 17563.

Such testimony reinforces the lack of guidance provided by the specification. It shows that the compounds, described as preferred embodiments, cannot be administered to a patient on a daily basis across the full scope of the dosage ranges disclosed. Thus, a skilled artisan would, at a minimum, be required to conduct further testing and screening to determine whether a claimed irreversible EGFR inhibitor can be dosed so as to not exceed any maximum tolerated dose threshold while still achieving a therapeutic effect. While the fact that inoperative embodiments are disclosed is not necessarily dispositive, this evidence weighs heavily in favor of non-enablement. *See Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*,

750 F.2d 1569, 1576–77 (Fed. Cir. 1984) ("[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." (citation omitted)).

The specification also accentuates its own shortcomings by describing the complexity and unpredictability of dosing the claimed "second generation" inhibitors; it is not as routine as Wyeth purports. *See* Oral Arg. at 3:46–50, Appeal No. 24–2325, available at https://www.cafc.uscourts.gov/oral-arguments/24-2325_05072026.mp3 (Wyeth counsel claiming that "there is nothing novel about the dosage range"); *id.* at 28:56–29:00 (Wyeth counsel arguing that the patents enable a skilled artisan to "dos[e] at conventional ranges"); *see also* Wyeth Op. Br. 39–43. The specification, however, reveals that determining the claimed "unit dosage" to achieve a therapeutic effect depends on several variable factors. It "depends on the subject to be treated, capacity of the subject's system to utilize the active ingredient, and degree of therapeutic effect desired," *id.* at col. 9 ll. 42–46, in addition to "the particular compound employed, the mode of administration and the severity of the condition being treated," *id.* at col. 8 ll. 55–57. The specification therefore concludes that the "[p]recise amounts of active ingredient required to be administered depend on the judgment of the practitioner and are peculiar to each individual." *Id.* at col. 9 ll. 44–46. Thus, the specification itself demonstrates that determining the claimed "unit dosage" is a complex and highly individualized task, while at the same time failing to provide the information and guidance necessary for a skilled artisan to perform that task without undue experimentation. And where, as here, the prior art is complex and unpredictable, the specification must provide correspondingly greater guidance. *See Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (claims not enabled where the specification provided only a starting point

for further research in an unpredictable field and required extensive screening and experimentation to identify operative embodiments).

Wyeth argues that the district court imposed a non-lethality requirement that AstraZeneca never advanced and that the evidence does not support. *See* Wyeth Op. Br. 36–43. Wyeth, however, mischaracterizes the district court's analysis. Again, the district court did not hold that the claims require proof that every claimed dosage be non-toxic, non-lethal, or satisfy any freestanding FDA clinical safety criteria. *See Decision*, 2024 WL 3823006, at *13. Rather, the court recognized that the claims require the daily administration of a "unit dosage" *to a human patient* and concluded that the specification fails to teach a skilled artisan how to determine such a dosage across the full scope of the claims. *Id.* at *15 ("Here, 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."). Evidence concerning toxic or lethal dosages was relevant not because the claims contain a toxicity limitation, but because that evidence demonstrated that the patents' disclosures provide little guidance as to which disclosed dosages, if any, are suitable for daily administration to a patient across the functionally claimed class of compounds. Here, as discussed, without teaching how to distinguish operative from inoperative embodiments, the specification leaves that task to the skilled artisan. *See* '314 patent col. 8 ll. 57–58. That is precisely the type of undue experimentation that the enablement requirement forbids. *See ALZA Corp.*, 603 F.3d at 941 ("[One] cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification."); *see also id.* at 943 ("Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (citation omitted)).

We recognize that it is accepted practice in patent law for one to be able to claim a method of treatment disclosing a range of doses to be administered, without showing actual clinical data, and leaving it to the FDA to ensure that approved products are safe and effective. *See United Therapeutics*, 74 F.4th at 1369. The problem with these patents is that, perhaps because of close prior art, their claims are limited to dosage forms to be administered to patients, yet they disclosed only a broad range of doses some of which were shown to be toxic, and they disclosed no actual dosages for any compound within the scope of the claims, thereby leaving it to a practitioner of the claims to perform undue experimentation.

In sum, we conclude that the district court did not err in granting JMOL of invalidity of the asserted claims of the '314 and '162 patents due to a lack of enablement.

CONCLUSION

We have considered Wyeth's remaining arguments but find them unpersuasive. For the foregoing reasons, we affirm the grant of JMOL of invalidity.

AFFIRMED