United States Court of Appeals for the Federal Circuit

ACTELION PHARMACEUTICALS LTD,
Plaintiff-Appellee

v.

MYLAN PHARMACEUTICALS INC.,
Defendant-Appellant

2022-1889

Appeal from the United States District Court for the Northern District of West Virginia in No. 1:20-cv-00110-JPB, Judge John Preston Bailey.

Decided: November 6, 2023

STEPHEN BLAKE KINNAIRD, Paul Hastings LLP, Washington, DC, argued for plaintiff-appellee. Also represented by IGOR VICTOR TIMOFEYEV; CHRISTOPHER P. HILL, AARON SELIKSON, SARAH SPENCER, MARK RUSSELL SPERLING, BRUCE M. WEXLER, New York, NY.

ERIC THOMAS WERLINGER, Katten Muchin Rosenman LLP, Washington, DC, argued for defendant-appellant. Also represented by TIMOTHY H. GRAY; JITENDRA MALIK, Charlotte, NC; DEEPRO MUKERJEE, LANCE SODERSTROM, New York, NY; JILLIAN SCHURR, Chicago, IL.

Before REYNA, STOLL, and STARK, *Circuit Judges*.

STOLL, *Circuit Judge*.

The issue on appeal in this patent case is the meaning of "a pH of 13 or higher." More specifically, the issue involves understanding what the significant digits are for "a pH of 13." The district court did not address extrinsic evidence, including textbooks, explaining how a person of ordinary skill in the art would view the significant digits for a pH value. Because this is a case where the district court must address the extrinsic evidence to understand how a person of ordinary skill in the art would understand the claim language, we vacate the district court's claim construction order with respect to the term "a pH of 13 or higher" and the judgment of infringement, and remand for the district court to consider the extrinsic evidence and its impact on claim construction.

BACKGROUND

The drug at issue in this Abbreviated New Drug Application (ANDA) litigation is epoprostenol, a naturally occurring substance that is useful for treating cardiovascular diseases. Epoprostenol was discovered in the early 1980s and was first brought to market under the brand name Flolan® in 1995. epoprostenol is unstable in water, it was prepared as a freeze-dried, or lyophilized, powder for use in the Flolan composition.

Actelion Pharmaceuticals LTD owns two patents—U.S. Patent Nos. 8,318,802 and 8,598,227—both directed to improved epoprostenol formulations.[1] According to the patent specification, there was a "need for epoprostenol

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[1] The patents are from the same family and have materially similar specifications. For ease, and consistent with the parties' briefing on appeal, we primarily cite the '802 patent.

formulations that can be reconstituted with commercially available IV fluids and do not require refrigeration after reconstitution until use." '802 patent col. 4 ll. 1–4. The inventor "unexpectedly found that epoprostenol solution in the presence of an alkalinizing agent, and high pH (>11) is very stable compared to Flolan." *Id.* at col. 4 ll. 8–10.

Claim 11 of the '802 patent is representative of the asserted claims:

> 11. A lyophilisate formed from a bulk solution comprising:
>
> (a) epoprostenol or a salt thereof;
>
> (b) arginine;
>
> (c) sodium hydroxide; and
>
> (d) water,
>
> wherein the bulk solution has *a pH of 13 or higher*, and wherein said lyophilisate is capable of being reconstituted for intravenous administration with an intravenous fluid.

Id. at col. 19 ll. 13–20 (emphasis on disputed term). The term "a pH of 13 or higher" appears in independent claims 1 and 11 of the '802 patent, and independent claims 16, 22, 32, and 40 of the '227 patent.

Actelion sells its epoprostenol product, an epoprostenol sodium for injection, under the brand name Veletri®. The '802 and '227 patents are listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book, as covering Veletri.

Mylan Pharmaceuticals Inc. sought approval to manufacture and sell a generic epoprostenol sodium for injection by filing an ANDA with the FDA. Its ANDA contained a certification that the '802 and '227 patents' claims were invalid or would not be infringed by the ANDA product. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). After receiving notice of

that certification, Actelion sued Mylan for infringement of claims 1, 6, 8, 10, 11, 16, 18, 20, and 22 of the '802 patent and claims 1–3, 8, 10, 12, 14, 16, 18–22, and 24–42 of the '227 patent. *See* 35 U.S.C. § 271(e)(2).

Relevant here, the parties dispute the meaning of the claim term "a pH of 13 or higher." Both parties proposed the plain and ordinary meaning of the term but disagreed on what that means. J.A. 85.

Actelion argued that "a pH of 13" in the context of the asserted claims is "a value of acidity that is given as an order of magnitude that is subject to rounding." *Actelion Pharms. LTD v. Mylan Pharms. Inc.*, No. 1:20-CV-110, Actelion's Redacted Opening Claim Constr. Br. 15–16, ECF No. 76 (*Opening Claim Constr. Br.*). More specifically, Actelion's proposal would allow a pH of 12.5, which rounds to 13, to read on the claim limitation of "a pH of 13 or higher." By contrast, Mylan argued that the proper construction cannot cover any pH values less than 13. *Actelion Pharms. LTD v. Mylan Pharms. Inc.*, No. 1:20-CV-110, Mylan Pharm. Inc.'s Responsive Claim Constr. Br. 1, ECF No. 75 (*Responsive Claim Constr. Br.*).

Actelion attacked Mylan's construction as, among other things, "chang[ing] the number of significant digits" and conflicting with the plain language of the claim. *Opening Claim Constr. Br.* 15. It explained that "[t]o describe a specific pH value, and not an order of magnitude, there would need to be a significant figure to the right of the decimal point or clear context to the contrary." *Id.* at 11. For support, Actelion cited three textbooks: Hans van Kessel et al., CHEMISTRY 12, Chapter 8.1 (2003) ("Kessel"), Frank Mustoe et al., CHEMISTRY 11, Chapter 10 (2001) ("Mustoe"), and Martin S. Silberberg, CHEMISTRY: THE MOLECULAR NATURE OF MATTER AND CHANGE, Chapter 18 (4th ed. 2006) ("Silberberg"). *Id.* at 11–12.

Mylan disagreed with Actelion's "ordinary rounding rules" and account of "significant figures." *Responsive Claim Constr. Br.* 1. But it explained that if the district

court were inclined to include measurement errors for a pH of 13, Actelion's three chemical textbooks support a narrower range of 12.995–13.004. *Id.* at 18–22 (citing J.A. 308 (Kessel); J.A. 343 (Mustoe); J.A. 402 (Silberberg)).

The textbooks explain how to calculate pH and identify significant figures for pH values. Silberberg explains that:

> As with any measurement, the number of significant figures in a pH value reflects the precision with which the concentration is known. However, it is a logarithm, so the number of significant figures in the concentration equals the number of digits *to the right of the decimal point in the logarithm*[.]

J.A. 400 (emphasis in original). Mustoe states: "How do you determine the number of significant digits in a pH? You count only the digits to the right of the decimal point." J.A. 339. Kessel echoes the same concept. *See* J.A. 304–05 (describing the formula for calculating pH, $pH = -\log([H^{+}_{(aq)}])$, and explaining that "the number of digits following the decimal point in the pH value is equal to the number of significant digits in the hydrogen ion concentration," the hydrogen ion concentration being $[H^{+}_{(aq)}]$).

The district court did not address this extrinsic evidence. Instead, it adopted Actelion's proposed construction based on the intrinsic record alone. *See Actelion Pharms. Ltd. v. Mylan Pharms. Inc.*, No. 1:20-CV-110, 2022 WL 446788, at *9 (N.D.W. Va. Feb. 14, 2022) (*Decision*). The court explained that the claims "consistently expressed 'a pH of 13' with two significant figures" and that the "claim language provides no basis for inferring any higher level of precision." *Id.* at *5. It reasoned that, "under its conventional significant figure meaning, the term a 'pH of 13' would ordinarily encompass those values that round up or down to 13, 12.5 to 13.4." *Id.* (citing *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1320 (Fed. Cir. 2007)).

Turning to the specification, the court concluded that "there is nothing to indicate that Actelion intended to import any higher degree of precision to 'a pH of 13' as it is articulated in the claims at issue." *Id.* at *7. Similarly, the court was "unpersuaded that the prosecution history requires it to read an increased degree of precision into the claim language." *Id.*

Lastly, the court engaged with *AstraZeneca AB v. Mylan Pharmaceuticals Inc.*, 19 F.4th 1325 (Fed. Cir. 2021). *Decision*, 2022 WL 446788, at *8–9. The district court distinguished *AstraZeneca*, reasoning that in this case, unlike *AstraZeneca*, "neither the specification nor prosecution history demonstrates that the inventor intended to employ a more precise level of exactness" for the claimed term. *Id.* at *8.

Following claim construction, the parties stipulated to final judgment of infringement in favor of Actelion. The district court entered the judgment on June 6, 2022.

Mylan appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

When a district court reviews only intrinsic evidence (i.e., the patent claims, specification, and prosecution history), its claim construction will amount solely to a ruling of law and will therefore be subject to de novo review. *See MasterMine Software, Inc. v. Microsoft Corp.*, 874 F.3d 1307, 1310 (Fed. Cir. 2017). In cases where the district court reviews extrinsic evidence to resolve factual disputes, such as the background science or the meaning of a term to a skilled artisan, however, those determinations must be reviewed under the clear error standard. *Id.* But the court's ultimate interpretation of the claim in light of the facts as found remains a conclusion of law subject to de novo review on appeal. *Id.*

The sole and narrow question before us involves the meaning of "a pH of 13 or higher," in the context of the '802

and '227 patents. Mylan argues that the claim term creates a floor at 13, beneath which the pH cannot fall. Appellant's Br. 3. In the alternative, Mylan argues that if a margin of error for a pH of 13 is needed, a pH of 13 would involve rounding to the hundredths place, encompassing 12.995–13.004. Reply Br. 12. In contrast, Actelion argues that the district court correctly construed the claim term as including rounding to the ones place, noting that "a numerical value includes rounding based on the inventor's selection of significant figures in the claims where the intrinsic record does not indicate otherwise." Appellee's Br. 26. As previewed, the intrinsic evidence is rather equivocal. At the same time, the extrinsic evidence relied on by the parties—but unconsidered by the district court—appears highly relevant to how a person of ordinary skill would understand the language "a pH of 13."

We start with the claim language. *See Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1276 (Fed. Cir. 2013) (explaining that we first, and primarily, rely on intrinsic evidence like the claims themselves when construing claim terms). The claim language, "a pH of 13 or higher," is a range with a specified lower limit. Based on this, Mylan argues that the lower end of the claimed range is not subject to the rules of rounding and that this court "has held that there is no need to 'read in an implicit range' because an 'open-ended range' like 'X and up' already expressly represents uncertainty at the top end." Reply Br. 10–11 (first citing *Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1581 (Fed. Cir. 1995); and then *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1292 (Fed. Cir. 2010)). We disagree with Mylan. That other cases have found precision in ranges specific to the claims at issue there, is not of great significance to our analysis here. In other words, there is no blanket rule that ranges, or specifically open-ended ranges, must foreclose rounding. This is especially true in this case where, though not expressly specified, there is in fact an upper limit in the claim because, as a matter of science, pH

values are often said to range from 0 to 14. *See, e.g.*, J.A. 340, 400.

Unlike other claim terms, the disputed claim term lacks approximation language like "about." *See, e.g.*, '802 patent col. 18 ll. 66–67 ("the bulking agent is present at *about* 1-10%" (emphasis added)); '227 patent col. 18 ll. 44–45 ("*about* –30 degrees C. at the rate of *approximately* 0.5 to 0.7 C./min." (emphases added)).

Based on this, Mylan argues that the absence of approximation language must mean that "a pH of 13" is *exactly* 13. Appellant's Br. 36–38. Otherwise, Mylan argues, "13" and "about 13" would both imply rounding, making the approximation language superfluous. Appellant's Br. 38 (citing *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 747, 752–53 (Fed. Cir. 2016) (applying the canon of construction that different terms have different meanings)). Indeed, we have held that a claim construction giving meaning to all terms in a claim is preferrable over one that does not. *See, e.g.*, *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1371–72 (Fed. Cir. 2005).

On the other hand, Actelion argues that rounding is required because approximation language like "about" signals different variations than those of rounding. *See* Appellee's Br. 34–35. Actelion also argues that "it is not practically possible to measure exact pH values" because to get an "exact" measurement "one would have to count every hydrogen ion in solution, which is not scientifically possible." Appellee's Br. 30 & n.8.

Ultimately, we do not find the absence of approximation language dispositive here. We reject any invitation to create a bright-line rule—either that language like "precisely" or "exactly" is always needed to avoid rounding or that the lack of approximation language, even when it may be found elsewhere in the claims, dictates a precise value. In other words, we find both views equally plausible here; that the absence of approximation language might suggest

no approximation, but that the nature of measuring a pH value might nonetheless reasonably require a margin of error.[2]

Finally, the claims do not recite just any measurement of 13 or higher; rather they are directed to a pH of 13 or higher. Thus, the district court should consider whether a pH of 13 carries any meaning to a person of ordinary skill in the art as regards precision of measurement, significant digits, or rounding. The parties submitted extrinsic evidence appearing to address this issue, but the district court did not discuss it.

We thus turn to the specification, which is "always highly relevant to the claim construction analysis," and "the single best guide to the meaning of a disputed term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Here, the specification reveals that the inventor inconsistently described the level of specificity for a pH of 13.

The specification explains that "[t]he pH of the bulk solution is preferably adjusted to about 12.5-13.5, most preferably 13." '802 patent col. 5 ll. 41–43. Mylan argues that this shows that the inventor (1) knew how to use approximation language when it wanted ("about 12.5-13.5") and chose not to for a pH of 13; (2) distinguished a pH value of "12.5" from that of "13"; and (3) distinguished a range ("12.5-13.5") from a definite value ("13"). Appellant's Br. 43–44. In other words, Mylan argues that "13" in "a pH of 13 or higher" cannot be an approximation or range of values, especially a range that encompasses 12.5. *Id.* Actelion counters, among other things, that "13" should allow rounding or else a preferred embodiment of the

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[2] Whether a pH value can be measured precisely—and to what degree—is a question of fact which we leave for the district court to determine in the first instance.

invention, meaning a pH of about 12.5 to 13.5, would be excluded from the claim scope. Appellee's Br. 42–43.

There is more. The specification seems to equate a pH of "13.0" to that of "13." Example 4 describes screening several "formulations with the pH of bulk solution . . . adjusted between 10.5 and 13.0." '802 patent col. 10 ll. 63–64. Tables 8 and 9 show the resulting stability data and display a bulk solution pH as "13" with no decimal point. Mylan argues that this shows that the inventor equated a pH of "13" with "13.0." Appellant's Br. 44–45. This may be so. But the specification uses both "13" and "13.0"—and various degrees of precision for pH values generally—throughout. *See, e.g.*, '802 patent col. 7 ll. 16–17 ("The pH of the bulk solution is adjusted to 13.0 with the base."), col. 11 l. 59 ("the pH of bulk solution adjusted to 13"), Tbl. 19 ("pH 11.58"). Said otherwise, the specification supplies the same clarity as to the desired level of precision as muddied water.

This specification stands in sharp contrast to that in *AstraZeneca*, which helped guide the claim construction at issue there. The issue in *AstraZeneca* was whether the concentration of PVP as "0.001%" meant 0.001% within one significant figure—encompassing a concentration of 0.0005% to 0.0014%—or a narrower meaning of precisely 0.001% with even more minor variations. 19 F.4th at 1329. The specification explained that stability was one of the most important factors when determining whether a compound could develop into a therapeutically useful pharmaceutical product. *Id.* at 1330. It made clear that a formulation comprising 0.001% w/w PVP is more stable than, and different from, a formulation with 0.0005% w/w PVP. *Id.* at 1332. Indeed, Figure 5 of the patent-at-issue showed that 0.0005% w/w PVP was one of the least stable formulations tested. *Id.* at 1331–32. Thus, the specification supported a claim construction that would exclude 0.0005% and focus on smaller variations. The data in the specification showed how slight differences in the

concentration of PVP, down to four decimal places, mattered for stability in the context of that invention. *Id.* at 1332.

To be sure, the issue here is also stability. But while the specification may state that "the stability of epoprostenol is better at pH 13 compared to lower pH samples," the specification does not evaluate the stability of epoprostenol at pH values between 12 and 13. '802 patent col. 11 ll. 54–56, Tbl. 8. So the specification does not show whether slight differences in the pH, at least between a pH of 12 and 13, matter for stability in the context of this invention. In sum, the scope of the claim term remains unclear even after consulting the specification.

We next turn to the prosecution history for guidance. The prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317 (citing *Vitronics*, 90 F.3d at 1582–83). Here, the prosecution history does not provide clarity.

The inventor amended the claim language at issue several times, including: "a pH of greater than 11," J.A. 116; "a pH of greater than 12," J.A. 126; and "a pH of at least 12," J.A. 144. The Examiner rejected the earlier claim language because they found that the prior art "teaches that their composition has a pH of at least 9 and the solutions are capable of being reconstituted to a pH of greater than 12, which encompasses pH of 13 and 14." J.A. 152. In the final rejection, the Examiner explained that the inventor had "not demonstrated that compositions with a pH of greater than 12 are superior to those of [a sample with a pH of 10.5], [but] they have demonstrated that for a pH of 13 there is a significant difference." J.A. 661. The inventor thereafter amended its claim from "a pH of greater than 12" to "a pH of 13 or higher." J.A. 177. The Examiner's reasons for allowance explained that the inventor "has

demonstrated unexpected results with respect to compositions made with solutions of pH 13 or higher as shown in tables 8 and 9 of the specification." J.A. 108. Specifically, "stability of the composition is greatly increased when reconstituted versus compositions with a pH of 12 or lower." *Id.* And that this "is an unexpected result as the prior art does not teach pH of 13 as having advantages over pH 11 or 12." *Id.*

In short, the prosecution history shows that the Examiner drew a distinction between the stability of a composition with a pH of 13 and that of 12. Such distinction, however, does not illuminate the narrower issue of whether a pH of 13 could encompass values that round to 13, in particular 12.5. Tables 8 and 9 simply do not compare compositions with pH values of 13 to those with a pH between 12 and 13.[3]

We find that this case is one where the proper claim construction cannot be reached without the aid of extrinsic evidence, and that the district court should have considered, at minimum, the textbook excerpts offered and addressed by the parties. The Supreme Court has made clear that there are cases where the district court must "look beyond the patent's intrinsic evidence and . . . consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the

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[3] Mylan also flags that the inventor conceded that the term "a pH of 13 or higher" was "duplicative" of "a pH of at least 13 or higher." Appellant's Br. 51; Reply Br. 10 (citing J.A. 97, 181). It argues that if the district court is correct that the phrase "greater than 13" draws a line forfeiting values below 13, then so too must the phrase "at least 13" and, thus, the inventor knew it claimed a floor of 13. Appellant's Br. 66 (citing *Decision*, 2022 WL 446788, at *7). We disagree. The term "greater than X" does not encompass "at least X." At minimum, the former excludes the value X while the latter includes it.

relevant art during the relevant time period." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331 (2015). And we have previously stated that "[o]nly if a disputed claim term remains ambiguous after analysis of the intrinsic evidence should the court rely on extrinsic evidence." *Pickholtz v. Rainbow Techs., Inc.*, 284 F.3d 1365, 1372–73 (Fed. Cir. 2002) (citing *Vitronics*, 90 F.3d at 1583). In such cases, the district court must "make subsidiary factual findings about that extrinsic evidence," and such findings are the evidentiary underpinnings of claim construction. *Teva*, 574 U.S. at 332. It is not for this court to make those findings in the first instance. We decline to decide, for example, how many significant figures "a pH of 13" has or what it would mean for a number—either for a pH value or for the concentration of hydrogen ions—to have zero significant figures. Instead, we leave those and other relevant factual questions that might arise based on the extrinsic evidence, including the three textbooks, for the district court to address in the first instance.

We have considered the parties' remaining arguments on appeal and find them unpersuasive.

CONCLUSION

For the reasons above, we vacate the district court's judgment of infringement, and remand for the district court to consider the extrinsic evidence and its impact on claim construction.

VACATED AND REMANDED

COSTS

No costs.