No. 2018-1691

United States Court of Appeals For the Federal Circuit

IDENIX PHARMACEUTICALS LLC, UNIVERSITA DEGLI STUDI DI CAGLIARI,
Plaintiffs-Appellants,
v.
GILEAD SCIENCES INC.,
Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware in Case No. 1:14-cv-00846-LPS, Chief Judge Leonard P. Stark

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CERTIFICATE OF INTEREST

Counsel for Appellants certifies the following:

1. The full name of every party represented by me is:

Idenix Pharmaceuticals LLC
Universita Degli Studi di Cagliari

2. The name of the real party in interest (not including any party identified in Question 3) represented by me is: None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Idenix Pharmaceuticals LLC: Merck & Co., Inc.
Universita Degli Studi di Cagliari: None.

4. The name of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Ashby & Geddes: Steven J. Balick, John G. Day, Andrew C. Mayo

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5. The title and number of any cases known to counsel to be pending in this or any other court or agency that may directly affect or be directly affected by this Court's decision in the pending appeal: None.

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STATEMENT OF COUNSEL

Overturning the jury's verdict, the panel held the claims (a) non-enabled based on the number of embodiments, disregarding even the panel's own acknowledgment that any needed experimentation was considered routine, and (b) inadequately described, because the specification's many embodiments did not expressly recite the infringing product. Based on my professional judgment, I believe this appeal requires answers to precedent-setting questions of exceptional importance:

1. Does the decision conflict with Section 112 and undermine genus claiming?

2. Does the decision conflict with the Seventh Amendment?

/s/ Gregory A. Castanias
Attorney for Plaintiffs-Appellants

INTRODUCTION

The panel's decision raises important questions about Section 112's disclosure requirements: It announces new enablement *and* written-description rules with profound consequences for genus claims, long acknowledged as essential to developing and protecting new medical treatments and urgently needed cures. Worse, these rules overtake the extensive factual underpinnings of Section 112, displacing the jury's historic, Seventh-Amendment-protected prerogative to find facts.

On enablement, the panel held that, where there are "at least many, many thousands of candidate compounds" for the genus, "many of which would require synthesis and each of which would require screening," "[t]hat constitutes undue experimentation" *as a matter of law*—without regard to the nature of the art or whether an ordinary artisan would view such synthesis and screening as a routine part of practicing the invention. Op. 20-21 (citing *Wyeth v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013)). As for written description, the panel held disclosure insufficient, *as a matter of law*, where it provides numerous examples and "possible" embodiments of the genus, yet the accused product—"the compound in question"—is "conspicuously absent." Op. 24.

If *Wyeth* compelled the panel's enablement analysis, then *Wyeth* was wrong and should be overruled; if not, the Court on rehearing should cabin *Wyeth* to its

facts to limit further damage to innovation. Either way, enablement is not a we-know-it-when-we-see-it question for judges to evaluate based on numbers. Nor can a patent be faulted, as the panel did here, for containing both too little disclosure for enablement, but too much for written description.

The decision also contravenes the statute and Supreme Court precedent by treating enablement as a question of law, *see Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n.6 (Fed. Cir. 1983), when the Supreme Court has held enablement "the right of the jury to determine." *Battin v. Taggert*, 58 U.S. 74, 85 (1854). And, contrary to the singular statutory requirement, the Court has dissected Section 112 into two separate inquiries, *see Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344-45 (Fed. Cir. 2010) (en banc). *See id.* at 1361-72 (dissenting opinions). This case is well-suited to revisiting these issues.

Regardless, the panel's new rules should be reconsidered. Whether Section 112 contains one requirement or two, or presents factual or legal inquiries, enablement and written description are now assessed *post hoc* by judges, not ordinary artisans. Judicial invalidation of patents based on the sheer potential number of embodiments, or for not disclosing the precise embodiment of the accused product, imposes more than a chilling effect on genus claiming. It threatens disaster for innovation.

BACKGROUND

Plaintiffs (together, "Idenix") invented a groundbreaking cure for Hepatitis C viral infection ("HCV"), transforming the entire industry. HIV and HBV treatments had been developed using chain-termination technology, where nucleosides bind to the viral machinery and terminate its replication in the body. Idenix identified the key for HCV chain-termination: using ribonucleosides with a methyl (CH_3) at their 2′-up position. Op. 5. Idenix correspondingly claimed:

> A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of *a purine or pyrimidine β-D-2'-methyl-ribofuranosyl* nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

The undisputed construction of the italicized language requires specific structures: (i) "a methyl group in the 2′ up position" of a ribonucleoside, and (ii) "non-hydrogen substituents at the 2′ down and 3′ down positions." Op. 6-7. That use of ribonucleosides with methyl at 2′-up is what Idenix discovered, and how Idenix claimed its invention. The field recognized Idenix's breakthrough, and developed their own 2′-methyl-up-ribonucleoside-based HCV treatments, within the scope of Idenix's claims. Appx37090(406:17-21); Appx37753(1993:5-14).

Gilead's product likewise has methyl at 2′-up. Gilead admitted infringement, as it had to. Op. 3. Gilead defended by challenging the patent's disclosure, but not for Idenix's breakthrough of using 2′-methyl-up

ribonucleosides. Instead, Gilead focused on the 2′-down position. Gilead's invalidity arguments previewed the panel's "too much, too little" fallacy: Gilead argued that there were too many embodiments to test, but that none of the extensive disclosure recited Gilead's product (with fluorine, a non-hydrogen substituent, at 2'-down). Op. 5-6.

At the 27-witness, 22-hours-per-side trial, the parties hotly disputed what the patent taught ordinary artisans. Though not its burden, Idenix presented scientific and real-world evidence that its disclosure taught its invention, using the genus of HCV-treating 2′-methyl-up ribonucleosides with non-hydrogen substituents (including fluorine) at 2′-down, and further taught how to make and use it, via copious "preferred" and "non-limiting examples." Appx77(15:28-29); Appx140(142:58-61). As for 2′-down in particular, the patent even listed three of the four other "halogens" besides fluorine—chlorine, bromine, and iodine. Appx75(12:55-61). Both sides' experts testified that the field was familiar with nucleoside chemistry and modification. Appx37735-37736(1921:3-1925:4); Appx37640(1727:18-1728:14). And Idenix's expert testified that the specification guided artisans in making and using embodiments. Appx37672-37673(1854:4-1859:1). Likewise, contemporaneous scholarship recognized Idenix's breakthrough discovery of a genus actually treating HCV; one of the authors

confirmed this at trial. Appx46660-46666; Appx46691-46703; Appx37752-37753(1990:1-1993:14).

In fact, Gilead's own bench chemist—not a person of ordinary skill in the art—used Idenix's patent to identify the infringing 2′-methyl-up, 2′-fluorine-down embodiment, and proceeded to make it using a well-known fluorination reaction. Op. 15. And in its requests for federal funding to pursue specific 2′-methyl-up compounds, Gilead even conceded the full scope of Idenix's invention—using HCV-treating ribonucleosides having methyl at 2′-up. Appx46617-46650(Appx46639); Appx46712-46766(Appx46734).

This type of evidence compelled the jury to reject Gilead's defenses and find it had "deliberately copied" Idenix's patent. Appx40(n.16); Op. 3. As to experimentation, even the panel agreed there was extensive evidence supporting the jury's implicit findings that "synthesis of an individual compound was largely routine" and "screening an individual compound for effectiveness was considered 'routine.'" Op. 15, 21. Put simply, the patent taught artisans how to quickly and effectively make and use 2′-methyl-up compounds that treat HCV.

Over a year later, the district court, citing *Wyeth*, set aside the jury's enablement verdict. The court held as a matter of law that the claims embraced too many embodiments not individually disclosed. Even so, the court rejected

Gilead's written-description defense (as it had twice before on summary judgment) because of disputed facts. Op. 3; Appx9; Appx21-56.

On Idenix's appeal, a 2-1 panel held Idenix's invention both non-enabled and insufficiently described, despite the jury's contrary findings on each.

ARGUMENT

The Court should return its Section 112 jurisprudence to the standard compelled by statute and Supreme Court precedent, grounded in whether the disclosure is enough for "any person skilled in the art." 35 U.S.C. § 112(a).

The panel, insensitive to that ordinary artisan, held the claims non-enabled as a matter of law, because "the number of candidate compounds to be tested" was too large, despite finding that synthesis and screening in the patent's art were both considered "routine." Op. 20. For written description, it paradoxically concluded the patent contained too much disclosure without specifically disclosing the infringing product, rendering the infringing product "conspicuously absent." Op. 24. Further, these holdings overtake the jury's constitutionally protected role to decide Section 112 facts.

Although the panel viewed its holdings as consistent with Circuit precedent and even "compelled" by *Wyeth*, its holdings contravene the statute, the Seventh Amendment, Supreme Court precedent, and the cited cases themselves. If *Wyeth* did compel the panel's decision, it should be overruled.

The decision's consequence is dire. It threatens genus claiming, even though "[c]laims to the genus of an invention . . . have long been acknowledged as patentable." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1313 (Fed. Cir. 2016).

I. THE PANEL'S DECISION CONTRADICTS SECTION 112 AND GOVERNING PRECEDENT

A. The Decision Significantly Distorts Enablement Law

The panel radically heightened the enablement standard. It felt "compel[led]" by a rule it discerned from *Wyeth*—that, if "practicing the full scope of the claims would require synthesizing and screening tens of thousands of candidate compounds for the claimed efficacy," the claim is non-enabled as a matter of law. Op. 20-21 (*Wyeth*'s "principle controls here."). Indeed, the district court has coined three recent enablement cases with the acronym "*WEI*" (after *Wyeth*; *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, 928 F.3d 1340 (Fed. Cir. 2019); and this case, *Idenix*). *MorphoSys AG v. Janssen Biotech, Inc.*, 358 F. Supp. 3d 354, 373-75 (D. Del. 2019). This now-cemented misunderstanding of enablement warrants correction.

The Supreme Court holds: "[I]t is enough if [the inventor] describes his method with sufficient clearness and precision to enable those skilled in the matter to understand what the process is, and if he points out some practicable way of putting it into operation." *The Telephone Cases*, 126 U.S. 1, 536 (1888). That is

the statute's "*quid pro quo*." *Universal Oil Prods. Co. v. Globe Oil & Ref. Co.*, 322 U.S. 471, 484 (1944). Accordingly, patents may "deal[] with a large class of substances" yet "leav[e] something to the skill of persons applying the invention." *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 271 (1916). This Court has likewise held: Patents need not "describe how to make and use every possible variant." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

Enablement does not turn on whether there are a lot of compounds in the genus or whether routine screening takes time. Patents "are written to enable those skilled in the art to practice the invention." *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). Enablement is not precluded by the necessity for some experimentation, such as routine testing." *Id.*

The question is whether the artisan's work in practicing the patent is routine (or, conversely, "undue"). Experimentation is a common part of the artisan's work and "does not preclude enablement." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (rejecting challenge based on Atlas's failure to list the "thousands of emulsions" covered by its claims, because "Du Pont's own researchers had little difficulty in making satisfactory emulsions" using the patent); *see also, e.g.*, *Minerals Separation*, 242 U.S. at 271 (upholding process with "infinite[]" embodiments as "clearly sufficiently definite to guide those skilled in the art"); *Crown Operations Int'l Ltd. v. Solutia Inc.*, 289 F.3d

1367, 1380 (Fed. Cir. 2002) (upholding claims where the artisan had "the necessary information to limit the claims to operative embodiments"); *In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) (rejecting challenge despite "thousands" of embodiments; the needed experimentation "to determine which catalysts will produce hydroperoxides would not be undue and certainly would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art'") (citation omitted).

The panel decision went against all these authorities, holding that, regardless of the artisan's skill and ordinary work, the genus had too many compounds to test, as a matter of law: "Because the claims of the '597 patent encompass at least many, many thousands of 2′-methyl-up nucleosides which need to be screened for HCV efficacy, the quantity of experimentation needed is large" and "constitutes undue experimentation." Op. 14, 21; *accord* Op. 20 ("The immense breadth of screening required . . . can only be described as undue experimentation."); Op. 19 (focusing on "size").

The panel's narrow, numerical approach contravenes the statute, in particular its central focus upon the "person skilled in the art." That is a factual issue, calibrated to the state of the art in the field, that must be resolved using various scientific and other evidence demonstrating the artisan's skill, knowledge, and routine activities and tools. In pharmaceutical and biotechnology fields,

synthesis and screening—even in large quantities—are routine, as they were here. Op. 15, 21. Specifications therefore typically enable genus claims using representative embodiments, just as Idenix's patent did, which is what the law had always required. Professor Robinson's "famous treatise" (*Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 862 (Fed. Cir. 1984)) shows how far afield the panel's ruling has strayed from the statute and prior law: "The applicant is not required to describe all possible forms" of his invention, "or even all such forms as he may have himself adopted"; "[t]hese belong to the skill of the mechanic, not the inventor; and having one embodiment before them, the public are presumed to be able to construct such others as they desire." William C. Robinson, THE LAW OF PATENTS § 485 (1890) ("ROBINSON ON PATENTS").

Wyeth is best viewed as an unexceptional application of settled precedent—Wyeth's specification disclosed only one operative embodiment, and Wyeth conceded there was *no* "guidance" *anywhere* suggesting other operative embodiments. 720 F.3d at 1385-86. *Wyeth* certainly did not compel the numbers-based decision in this case.

However this new approach came about, it is both wrong and destructive to innovation. Genus claims are at the heart of breakthrough medical treatments, and will almost always yield "at least thousands" of embodiments. The new "numbers" test is hostile to genus claiming at an unacceptable cost, particularly

where the only criticism of the patent is that routine testing on the order of thousands of embodiments may be required. "Thousands" may sound like a painstaking number to a non-artisan, but that impression disregards ordinary tools and routine work.

The facts here demonstrate the problem. Idenix made an undeniable contribution, and claimed precisely commensurate: using ribonucleosides having methyl at 2′-up to treat HCV. *As even the panel found*, substantial, real-world evidence showed that identifying operative embodiments and eliminating inoperative ones simply involved *routine synthesis and screening*. *Supra* pp. 4-6. And Gilead (which bore the burden) presented *no evidence* that any significant portion of 2′-methyl-up ribonucleosides (if any at all), including variations at 2′-down, would stymie the artisan by not working. To the contrary, Gilead documents and witnesses showed that practicing the claims was routine. *Supra* p. 6. Idenix gave the world the patent bargain's *quid*, but the panel eviscerated the *quo*.

Narrowing claims to a few particular embodiments (as the dissent seemed to suggest) is no solution. "A potential infringer could readily avoid 'literal' infringement … by merely finding another analogous" embodiment. *Angstadt*, 537 F.2d at 503. "[T]he Wright brothers invented a single wooden glider that could barely fly," yet "their tremendous social contribution," one "reflected in both their

original glider and modern F-117 jets," "calls for a large reward"; "[o]therwise, an unscrupulous pirate can copy the idea while changing the form." Tun-Jen Chiang, *The Levels of Abstraction Problem in Patent Law*, 105 Nw. U. L. Rev. 1097, 1098, 1104, 1115 (2011). No wonder commentators immediately noted the threat the panel's decision poses. *E.g.*, Valerie Bauman, *Merck's Patent Loss to Gilead May Have Big Impact on Drugmakers*, Bloomberg Law (Oct. 31, 2019), *available at* https://news.bloomberglaw.com/pharma-and-life-sciences/mercks-patent-loss-to-gilead-may-have-big-impact-on-drugmakers.

B. The Decision Significantly Distorts Written-Description Law

The panel decision also harms written-description law. Even if Section 112's singular command permits two tests, the panel erroneously confined "written description" to whether the patent discloses too many examples without disclosing "the compound in question," *i.e.*, the particular accused product. Op. 24-25 ("In light of the conspicuous absence of that compound, a POSA would not 'visualize or recognize the members of the genus'" as including it.) (citation omitted). As a result, the panel held—as a matter of law—that "similarities" among disclosed examples and the accused product are somehow not enough. Op. 25. This hostility to disclosure-by-example contradicts Section 112.

Section 112 requires "a written description of the invention," not all embodiments, nor, specifically, "the compound in question." The jury was

accordingly instructed: "The full scope of a claim or any particular requirement in a claim need not be expressly disclosed ...." Appx177. *Ariad* makes clear that disclosure of "a representative number of species falling within the scope of the genus or structural features common to the members of the genus" is sufficient. 598 F.3d at 1350. The point is to "ensure[] that the public receives a meaningful disclosure in exchange for being excluded from practicing an invention for a period of time." *Id.* at 1354. Written description does not require the recitation of any specific embodiment, such as the accused product. *See id.* at 1352.

The panel's test conflicts with this law. Although the panel was purportedly "mindful of *Ariad*'s caution that written description does not require 'a nucleotide-by-nucleotide recitation of the entire genus,'" and instead "relatively few representative examples or formulas" can "support a claim on a structurally similar genus," the panel's holding that this principle "does not extend to this case," Op. 24, is inexplicable. Just like its enablement ruling, the panel's we'll-know-it-when-we-see-it test for how many examples, without specifically naming the accused embodiment, is too many, improperly leaves the determination to *post hoc* panel review and disregards the skilled artisan. It also creates perverse incentives for applicants to detail, rather than "preferably omit[]," what is known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Idenix's invention was using ribonucleosides with a methyl at 2′-up on their sugar ring. For substituents at 2′-*down* (the only position at issue), expert and fact evidence showed that Idenix's disclosed embodiments and representative examples objectively would, and actually did, blaze the trail for ordinary artisans to routinely use compounds within the genus. *Supra* p. 4-6. Specific disclosure of the infringing species, or of any other species beyond the patent's disclosure, was unnecessary.

No reasonable applicant, at least prior to this decision, would have expected a detailed disclosure of embodiments "similar[]" to the accused product (Op. 25) to be legally inadequate. Any interpretation of the decision short of this is equally problematic; the lack of clarity leaves the innovation communities at sea as to what disclosure will be sufficient.

II. THE PANEL'S DECISION NEGATES THE JURY'S CONSTITUTIONALLY PROTECTED ROLE IN DECIDING DISCLOSURE ISSUES ON GENUINELY DISPUTED EVIDENCE

Professor Robinson long ago described the foundational rule that "[t]he sufficiency of the Description is a question of fact, to be investigated by experience, elucidated by evidence, and decided by a jury." ROBINSON ON PATENTS § 503. The panel's decision guts this proper role for the jury.

Written description is a fact question; the jury, having heard the evidence and observed the witnesses, determines what the specification teaches ordinary

artisans and whether the defendant has shown that the invention is not sufficiently described. *See Ariad*, 598 F.3d at 1353-54. The district court twice denied summary judgment, and again denied JMOL, because there were disputed written-description facts—which the jury then decided for Idenix.

The panel simply ignored the jury's finding. It never mentioned the jury or its verdict, Gilead's high clear-and-convincing-evidence burden, or the Court's limited substantial-evidence review of such fact determinations. Op. 21-25. Instead, it decided the issue *de novo*—asking for itself "whether the specification demonstrates possession of the 2′-methyl-up 2′-fluoro-down nucleosides that are the basis for Gilead's accused product." Op. 22.

Under this decision, the jury's right to decide written description evaporates where, in a judge's (not an ordinary artisan's) opinion, the specification discloses *too many* compounds without also disclosing the infringing one. *See supra* pp. 13-15. Consequently, factual written-description questions for pharmaceutical and biological claims—which often involve classes of compounds—will be resolved by judges, not juries.

The decision will have similar consequences for enablement. The Supreme Court has long held it is "the right of the jury to determine, from the facts in the case," whether a specification is "so precise as to enable any person skilled in the structure of machines, to make the one described [in the patent]," *Battin v. Taggert*,

58 U.S. 74, 85 (1854), or whether, instead, the defendant has shown the patent not "sufficiently definite to guide those skilled in the art to its successful application." *Minerals Separation*, 242 U.S. at 271; *Loom Co. v. Higgins*, 105 U.S. 580, 586-87 (1881) (patent held enabled based on fact evidence); *see also U.S. Bank Nat'l Ass'n ex rel. CWCapital Asset Mgmt. LLC v. Vill. at Lakeridge, LLC*, 138 S. Ct. 960, 967 (2018) ("[M]ixed questions immers[ing] courts in case-specific factual issues" should be treated as questions of fact, not law.). Before 1982, regional circuits were largely in accord; the "adequacy of the published description" was a question "of fact," "not a question of law." *Bros Inc. v. Browning Mfg.*, 317 F.2d 413, 416 (8th Cir. 1963); *see also, e.g.*, *Refrigeration Patents Corp. v. Stewart-Warner Corp.*, 159 F.2d 972, 975 (7th Cir. 1947); *A. B. Dick Co. v. Barnett*, 288 F. 799, 800 (2d Cir. 1923). Once a jury resolves a fact, it may not be reexamined beyond the common law's strictures. *See Baltimore & Carolina Line, Inc. v. Redman*, 295 U.S. 654, 657 (1935).

This Court, relying on *administrative* C.C.P.A. precedent, has (mistakenly) held enablement a legal conclusion. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n.6 (Fed. Cir. 1983). But it has still repeatedly acknowledged that this conclusion turns on "a factually intensive inquiry regarding the amount of experimentation required." *AK Steel*, 344 F.3d at 1245; *Crown*, 289 F.3d at 1381 ("[A]mount and type of experimentation required" are "facts that will determine

whether such experimentation is undue."); *Wands*, 858 F.2d at 737 ("conclusion reached by weighing many factual considerations"); *Bio-Technology Gen. Corp. v. Genentech, Inc.*, 267 F.3d 1325, 1330-31 (Fed. Cir. 2001) ("the province of the trier of fact" to resolve disputes "[w]hen scientific certainty is not available").

The panel's decision leaves little room for the jury's historic fact-deciding authority. The panel reversed implicit jury findings on five of seven *Wands* factors—quantity of experimentation, working examples, other guidance in the patent, predictability in the field, and claim scope—and scores of subsidiary findings. Op. 8-20. It repeatedly imposed its view over reasonable choices a jury could have made, often in language reminiscent of a claim-construction inquiry—evaluating the patent document to the exclusion of other relevant, genuinely disputed evidence, and disregarding Gilead's (high) burden of proof. *E.g.*, Op. 14 (reciting testimony on "unpredictab[ility]," without accounting for contrary testimony and evidence, *see supra* pp. 4-6); Op. 13-19 (discussing NS5B). Even more perplexingly, the panel held the claims non-enabled despite agreeing that a jury could—as this jury did—conclude that an artisan could routinely make and screen compounds. Op. 20-21. In short, claims can now be non-enabled "as a matter of law" because judges, not skilled artisans, view the patent alone and conclude that it simply covers too many compounds.

Enablement is not mere document interpretation. It is a broader factual

inquiry into how the patent speaks to and directs the ordinary artisan. On this question, too, the decision improperly transfers authority from juries, where the Seventh Amendment reposes this obligation, to judges.

CONCLUSION

The rules for determining adequate disclosure are among the most critical in our patent laws. This case, decided on a full trial record with no waiver or preservation issues, presents an ideal vehicle for the en banc Court to restore the proper balance between disclosure and patents, and between jury fact-finding and court review.

Dated: January 15, 2020

Respectfully submitted,

/s/ Gregory A. Castanias

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ADDENDUM

United States Court of Appeals for the Federal Circuit

IDENIX PHARMACEUTICALS LLC, UNIVERSITA DEGLI STUDI DI CAGLIARI,
Plaintiffs-Appellants

v.

GILEAD SCIENCES INC.,
Defendant-Appellee

2018-1691

Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-00846-LPS, Chief Judge Leonard P. Stark.

Decided: October 30, 2019

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for plaintiffs-appellants. Also represented by JENNIFER LORAINE SWIZE; LISA LYNN FURBY, Chicago, IL; CALVIN GRIFFITH, RYAN BOYD MCCRUM, Cleveland, OH; ANTHONY INSOGNA, San Diego, CA; JEFFREY A. LAMKEN, SARAH JUSTINE NEWMAN, MICHAEL GREGORY PATTILLO, JR., MoloLamken LLP, Washington, DC.

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MOULTON, Menlo Park, CA; BRIAN PHILIP GOLDMAN, San Francisco, CA; ERIC SHUMSKY, Washington, DC; FRANK SCHERKENBACH, Fish & Richardson, PC, Boston, MA; CRAIG E. COUNTRYMAN, W. CHAD SHEAR, JONATHAN ELLIOT SINGER, San Diego, CA.

Before PROST, *Chief Judge*, NEWMAN and WALLACH, *Circuit Judges*.

Opinion for the court filed by *Chief Judge* PROST.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

PROST, *Chief Judge*.

Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement and hold that the patent is also invalid for lack of written description.

I

This appeal stems from Idenix's December 2013 patent infringement suit against Gilead, originally filed in the U.S. District Court for the District of Massachusetts and later transferred to the District of Delaware. J.A. 259–69. At the time of the suit, both Idenix and Gilead were researching and developing drugs for treatment of the hepatitis C virus ("HCV"). HCV is a leading cause of chronic liver disease, infecting hundreds of millions of people worldwide, and accounting for tens of thousands of

deaths per year in the United States alone. Idenix alleged that the imminent Food and Drug Administration approval, and launch, of Gilead's HCV treatment drug sofosbuvir would infringe Idenix's U.S. Pat. No. 7,608,597 (the "'597 patent").

Following years of litigation, Chief Judge Stark held a two-week jury trial in December 2016. Gilead stipulated to infringement under the district court's claim construction but argued that the '597 patent was invalid for failure to meet the written description and enablement requirements. The jury found for Idenix, upholding the validity of the patent and awarding damages. After trial, Gilead filed a renewed motion for JMOL with respect to written description and enablement. The district court denied the motion with respect to written description but granted JMOL on enablement, holding the '597 patent invalid.

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

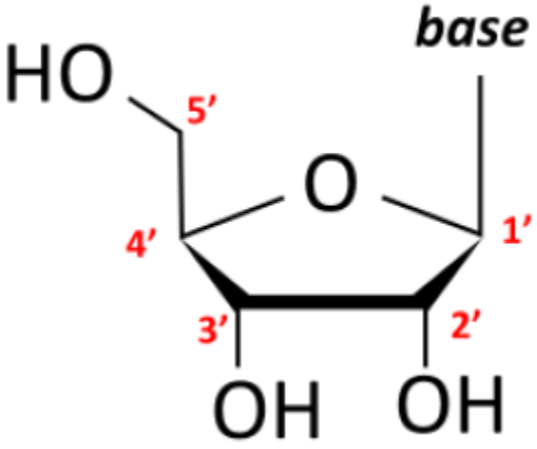
II

We review the denial or grant of a motion for JMOL under regional circuit law. *See Tr. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1361 (Fed. Cir. 2018). Applying Third Circuit law, we "exercise plenary review over a district court's rulings on motions for JMOL, applying the same standard as the district court." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1341–42 (Fed. Cir. 2008) (citing *Gagliardo v. Connaught Labs., Inc.*, 311 F.3d 565, 568 (3d Cir. 2002)). A grant of JMOL is appropriate "where a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have had a legally sufficient evidentiary basis to find for the party on that issue." *Id.* at 1342; *see* Fed. R. Civ. P. 50(a).

Enablement requires that "the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled when, "at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Whether a claim satisfies the enablement requirement is a question of law that we review de novo. *Tr. of Boston Univ.*, 896 F.3d at 1361. However, "in the context of a jury trial, we review the factual underpinnings of enablement for substantial evidence." *Id.*

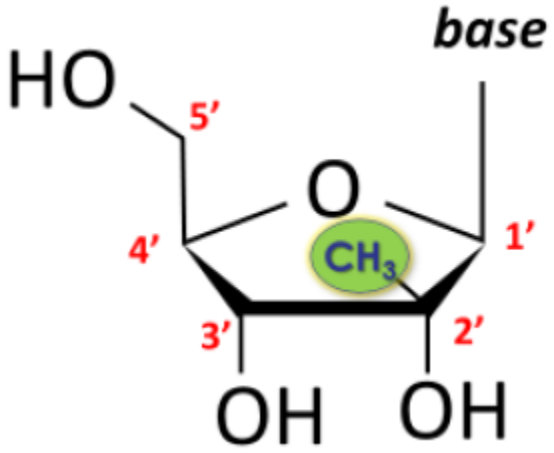
III

The '597 patent claims a method of treating HCV by administering nucleoside compounds having a specific chemical and stereochemical structure. The nucleosides claimed in the '597 patent contain a sugar ring having five carbon atoms, numbered 1' (one prime) to 5' (five prime), as well as a base. At each carbon, substituent atoms or groups of atoms can be added in either the "up" or "down" position. This structure is illustrated below, with a hydroxyl group (OH) shown attached at the 2'-down and 3'-down positions:



Appellant's Br. 8. The parties' arguments focus on the presence of various possible substituents at the 2'-up and 2'-down positions.

Idenix argues that the key to its invention, and to treatment of HCV, is the use of 2'-methyl-up nucleosides: nucleosides "having a methyl substitution ('CH3') at the 2' 'up' position of the molecule's sugar ring," illustrated below.



Appellant's Br. 7–8.

Gilead argues that this characterization is overly broad, as the '597 patent provides no guidance in determining which of the billions of potential 2'-methyl-up nucleosides are effective in treating HCV. *See* Appellee's Br. 8. According to Gilead, the '597 patent primarily describes 2'-methyl-up nucleosides that have a hydroxyl group (OH) at the 2'-down position. But Gilead's accused product has fluorine (F), not OH, at the 2'-down position. *Id.* According to Gilead, the '597 patent cannot enable the full scope of effective 2'-methyl-up nucleosides at least because its accused embodiment, 2'-methyl-up 2'-fluoro-

down, is not disclosed in or enabled by the specification.[1]

The only independent claim of the '597 patent recites:

> 1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine ß-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

'597 patent claim 1. The district court construed the structural limitation "ß-D-2'-methyl-ribofuranosyl nucleoside" to require "a methyl group in the 2' up position and non-hydrogen substituents at the 2' down and 3' down positions." *Idenix Pharm., Inc. v. Gilead Scis., Inc.*, 2015 WL 9048010, at *6 (D. Del. Dec. 16, 2015) ("Claim Construction Order"). Thus, while the claim requires methyl at the 2'-up position, it allows nearly any imaginable substituent at the 2'-down position.[2]

At Idenix's urging, the district court also construed the preamble, "[a] method for the treatment of a hepatitis C virus infection," as a narrowing functional limitation. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2016 WL 6802481, at *5 (D. Del. Nov. 16, 2016). In combination with the requirement to administer an "effective amount," this claim language "limit[s] the scope of the claims to the use of some set of compounds that are effective for treatment of HCV." *Id.* at *6.

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[1] We have previously held that an Idenix patent on similar technology failed to enable 2'-methyl-up 2'-fluoro-down nucleosides, albeit in a different procedural posture. *See Storer v. Clark*, 860 F.3d 1340 (Fed. Cir. 2017).

[2] Neither party contends that the sole limitation on 2'-down, which excludes hydrogen substituents, is significant in this appeal.

Neither party challenges the district court's claim constructions in this appeal. Claim 1, therefore, encompasses any β-D nucleoside meeting both the structural limitations (including a methyl group at 2'-up) and the functional limitations (efficacy in treating HCV). It is undisputed, however, that there are billions of potential 2'-methyl-up nucleosides. The key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which 2'-methyl-up nucleosides would be effective for treating HCV. We conclude that they would not.[3] Taking into account

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[3] The dissent, making an argument not advanced by Idenix at trial or before us, reaches the opposite conclusion only by disregarding the district court's binding claim construction, ignoring the resulting stipulation of infringement, and analyzing a case that is not the one presented to us.

Before the district court, Gilead proposed a narrow claim construction that required "hydroxyl groups at the 2' down and 3' down positions." Claim Construction Order at *6. Because Gilead's accused product has fluorine at 2'-down, rather than a hydroxyl group, this would have resulted in non-infringement. However, the district court expressly rejected that proposal, instead adopting a broader construction that allowed for any "non-hydrogen substituents," including fluorine. *Id.* On the basis of that broad construction, Gilead stipulated to infringement, and the parties held a trial solely on invalidity. J.A. 6. Neither side challenged the claim construction on appeal, and the issue is not before us.

The question before us is whether the '597 patent enables the full scope of its claims under the district court's broad construction. The dissent declines to answer that question, and instead applies its own "narrow" claim construction, under which only hydroxyl groups are permitted at the 2'-down position. Dissent at 3; *id.* at 7 (limiting

the evidence presented at trial, a reasonable jury would not have had a legally sufficient basis to find otherwise.

In analyzing undue experimentation, we consider the factors first enumerated in *In re Wands*. The uncontested jury instructions in this case formulate the *Wands* factors as follows:

> (1) the quantity of experimentation necessary;
>
> (2) how routine any necessary experimentation is in the relevant field;
>
> (3) whether the patent discloses specific working examples of the claimed invention;
>
> (4) the amount of guidance presented in the patent;
>
> (5) the nature and predictability of the field;
>
> (6) the level of ordinary skill; and

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claim to where "R^7 is OH"); *id.* at 12 ("narrow formula of three OH groups and a CH_3 group as pictured"). In essence, the dissent adopts Gilead's rejected claim construction. Indeed, the dissent admits that under its new claim construction, Gilead's accused product "is not within the scope of the claims." Dissent at 15.

We agree with the dissent that, under a narrower construction, the claims of the '597 patent might well be enabled, and the accused product would not infringe. But that is not the case before us. We are tasked with deciding whether the claims, *as construed*, are enabled. The dissent appears to agree with us that they are not. Dissent at 12 ("the '597 specification did not describe and enable products other than . . . the narrow formulas of three OH groups"). But rather than answer that question, the dissent has applied its newly invented claim construction to find a hypothetical narrower claim valid but not infringed. Respectfully, that is no way to conduct an appeal.

(7) the scope of the claimed invention.

J.A. 179; *see Wands*, 848 F.3d at 737. The parties agree that the level of ordinary skill in the art is high, but dispute the impact of the remaining factors. We discuss each in turn.

A

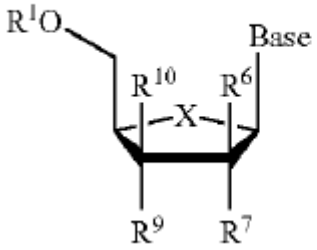
We agree with the district court that the quantity of experimentation required to determine which 2'-methyl-up nucleosides meet claim 1 is very high, which favors a finding of non-enablement. The evidence presented to the jury could not support any other finding. At trial, Gilead presented expert testimony that because the claim allows for nearly any substituent to be attached at any position (other than 2'-up), a person of ordinary skill in the art would understand that "billions and billions" of compounds literally meet the structural limitations of the claim. J.A. 37545.

Idenix did not dispute that math, but argued to the jury that this approach was merely "theoretical," because a person of ordinary skill in the art ("POSA") would not attach substituents at random. *See* J.A. 37734. Instead, Idenix argued, a POSA would know to "take into account the patent as a whole" to focus on a "significantly smaller" set of candidate compounds. *Id.* The district court accepted this argument, but concluded that even taking into account the knowledge and approach of a POSA, the candidate compounds number "likely[] millions or at least many, many thousands." JMOL Opinion, at *12.

On the evidence presented, a reasonable jury could only have concluded that at least "many, many thousands" of candidate compounds exist. Idenix's evidence, which supports at best an unspecified number "significantly smaller" than "billions," could not lead a reasonable jury to any other conclusion. As Gilead points out, even hundreds of millions is a "significantly smaller" number when the

starting point is "billions and billions." Appellee's Br. 35–36. Idenix's counsel conceded that in its "best case," considering the knowledge of a POSA, the structural limitations still encompass "some number of thousands" of compounds. J.A. 40013.

This conclusion is supported by the '597 patent itself, which discloses enormous quantities of 2'-methyl-up nucleosides that would need to be tested for efficacy against HCV. The specification contains 18 Formulas, each of which is represented by a diagram with variables at multiple positions. For example, Formula XVII, described as the "eleventh principal embodiment," provides:

> a compound of Formula XVII, or a pharmaceutically acceptable salt or prodrug thereof:
>
> (XVII)
>
> 
>
>
> wherein:
>
> Base is a purine or pyrimidine base as defined herein;
>
> R^1 and R^2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a

> cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1 or R^2 is independently H or phosphate;
>
> R^6 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, —C(O)O(alkyl), —C(O)O(lower alkyl), —O(acyl), —O(lower acyl), —O(alkyl), —O(lower alkyl), —O(alkenyl), chloro, bromo, fluoro, iodo, NO_2, NH_2, —NH(lower alkyl), —NH(acyl), —N(lower alkyl)$_2$, —N(acyl)$_2$;
>
> R^7 and R^9 are independently hydrogen, OR^2, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, —C(O)O(alkyl), —C(O)O(lower alkyl), —O(acyl), —O(lower acyl), —O(alkyl), —O(lower alkyl), —O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, —NH(lower alkyl), —NH(acyl), —N(lower alkyl)$_2$, —N(acyl)$_2$;
>
> R^{10} is H, alkyl (including lower alkyl), chlorine, bromine or iodine;
>
> alternatively, R^7 and R^9, or R7 and R^{10} can come together to form a pi bond; and
>
> X is O, S, SO_2 or CH_2.

'597 patent col. 12 ll. 20–67. The 2'-up position in this formula, represented as R^6, includes a methyl group as one of two dozen possible substituents.[4] Even limiting this formula only to its 2'-methyl-up variations, however, the formula provides more than a dozen options at the R^1 position, more than a dozen independent options at the 2'-down position, more than a dozen independent options at the 3'-

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[4] The term "alkyl" is defined in the '597 patent to include methyl. '597 patent col. 37 ll. 9–25.

down position, and multiple independent options for the base.

As the district court meticulously calculated, this formula alone discloses more than 7,000 unique configurations of 2'-methyl-up nucleosides. JMOL Opinion, at *12.[5] Other formulas in the specification provide equally large numbers of compounds. Idenix argues that a POSA would have focused on only a narrow subset of billions of possible candidates, but the jury was not free to adopt a number lower than the many, many thousands of configurations identified as "principal embodiment[s]" in the patent itself. *See, e.g.*, '597 patent col. 12 ll. 20–22. Testing the compounds in the specification alone for efficacy against HCV requires enough experimentation for this factor to weigh in favor of non-enablement.

Idenix relatedly argues that a POSA would understand the "focus" of the claim to be "the inhibition of the NS5B polymerase" to effectively cure HCV. Appellant's Br. 16.

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[5] This figure is conservative, as the district court noted. JMOL Opinion, at *12 (noting that "Formula XVII on its own constitutes *at least* a minimum of approximately 7,000 unique configurations" (emphasis added)). The number of candidates disclosed by this formula is likely orders of magnitude higher. For example, the district court's calculation considered "alkyl" to be one possible option at each position. But the specification defines "alkyl" to include at least twenty distinct options that could be substituted. '597 patent col. 37 ll. 9–26. The terms "purine or pyrimidine base" and "acyl" are similarly each defined to include at least twenty independent options. *See id.* at col. 37 l. 59–col. 38 l. 29; JMOL Opinion, at *12 n.11 ("The number of possible configurations increases considerably (by an order of magnitude) when all the compounds the patent defines as a purine or pyrimidine base are taken into account.").

Therefore, Idenix argues, a POSA would know which candidates were likely to inhibit NS5B, and would test only those, resulting in a "predictable and manageable" group of candidate compounds. *Id.* This argument improperly attempts to narrow the claim to only those nucleosides that would inhibit the NS5B polymerase. But the district court's claim construction, not challenged in this appeal, made clear that "as a matter of law, NS5B activity is ***not*** a claim limitation." JMOL Opinion, at *26 (emphasis in original).

Moreover, it would be improper to rely on a POSA's knowledge of NS5B to fill the gaps in the specification. "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." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Idenix's attempt to treat NS5B as a claim limitation, based on the knowledge of a POSA, would be an impermissible end-run around the requirement to enable the full scope of the claim.[6]

At oral argument here on appeal, Idenix presented an additional theory for why little or no experimentation was required. According to Idenix, "the jury could have concluded that ***all*** 2'-methyl-up ribonucleosides were active against the hepatitis C virus, so that the numbers don't matter. Screening [of each candidate for efficacy against HCV] was irrelevant." Oral Arg. at 6:07–6:18, No. 2018-1691, http://www.cafc.uscourts.gov/oral-argument-

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[6] Idenix does not argue that the full scope of the claim includes only compounds that inhibit the NS5B polymerase. Nor could it, as the '597 patent describes treating HCV in other ways. *See* '597 patent col. 139 ll. 30–32 ("Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, or by inhibiting other enzymes needed in the replication cycle, or by other pathways.").

recordings. We do not agree that the evidence presented could have supported this conclusion. Indeed, Idenix's own evidence contradicts it.

At trial, Idenix's expert agreed that the field of modifying nucleosides for anti-HCV activity was "in its infancy" and "unpredictable." J.A. 37736. Another of Idenix's experts testified that screening was performed to "actually cut down on the number of compounds, by removing all inactive ones to a few interesting ones." J.A. 37747. A third Idenix expert testified that "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it." J.A. 37411. And at oral argument on the post-trial motions, Idenix's counsel agreed that "not all 2' methyl up ribonucleosides will be effective to treat HCV," and therefore screening was necessary. J.A. 40007; *see also id.* ("But would one have to do some screening? Certainly.") In light of this evidence, and this concession, no reasonable jury could have concluded that all 2'-methyl-up nucleosides were effective against HCV or that no screening was needed.

Because the claims of the '597 patent encompass at least many, many thousands of 2'-methyl-up nucleosides which need to be screened for HCV efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement.

B

The district court concluded that a reasonable jury could only find that many candidate nucleosides would need to be synthesized before they could be screened, as not all candidate nucleosides were available for purchase. We agree.

Idenix argues that "a significant number of nucleosides were available off-the-shelf in libraries." Appellant's Br. 40. However, in light of the billions of possible 2'-methyl-up nucleosides, or even the many, many thousands of

nucleosides that meet the formulas provided in the patent, no reasonable jury could conclude that "a significant number" of available nucleosides removes the need for synthesis. Moreover, Idenix's expert testified that synthesis was often required even when starting with a compound purchased from a library or database. *See* J.A. 37735 ("the general approach is starting from an intact nucleoside that you can buy . . . and then you start doing chemistry on this intact nucleoside and modify the nucleoside structure in the sugar part or even the base part"). In light of this evidence, a reasonable jury could only have found that synthesis was necessary.[7]

We do agree with Idenix, however, that a jury could have found that the synthesis of an individual compound was largely routine. Gilead argued that synthesis was difficult, presenting the jury with evidence of an Idenix scientist who repeatedly tried and failed to synthesize 2'-methyl-up 2'-fluoro-down, which is the nucleoside at issue in Gilead's accused product. *See* JMOL Opinion, at *16. Idenix countered this with evidence of a scientist at a Gilead subsidiary who produced a 2'-methyl-up 2'-fluoro-down compound "in relatively short order." *See id.* As a reviewing court, "we are mindful that we 'may not weigh the evidence, determine the credibility of witnesses, or substitute [our] version of facts for the jury's version.'" *Agrizap*, 520 F.3d at 1342 (quoting *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)). In light of this conflicting testimony, a reasonable jury was entitled to conclude that a POSA could synthesize this particular compound in relativity short order.

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[7] Our analysis does not rely on the contested statement in the district court's opinion as to whether or not Idenix's expert expressly testified that "not all compounds of interest were commercially available." JMOL Opinion, at *15.

Because a jury could only have found that synthesis of many 2'-methyl-up nucleosides was necessary, but could have concluded that synthesis of an individual nucleoside was largely routine, this factor weighs against a finding of non-enablement.

C

We analyze the presence of working examples and the amount of guidance presented in the specification together. Idenix argues that these factors weigh against non-enablement because the specification "identifies the 'key' modification (2'-methyl-up)" and contains "working examples of active 2'-methyl-up ribonucleosides that were tested." Appellant's Br. 44. We disagree.

Idenix contends that the '597 patent provides meaningful guidance as to which nucleosides meet the functional limitations of the claim because it identifies the "key" modification of 2'-methyl-up. Appellant's Br. 44. That is insufficient. An enabling disclosure must "be commensurate in scope with the claim." *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983). Claim 1 requires more than just an identification of 2'-methyl-up: it requires identification of which 2'-methyl-up nucleosides will effectively treat HCV. Without specific guidance on that point, the specification provides "only a starting point, a direction for further research." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010). That guidance is absent from the '597 specification.

Idenix argues that the '597 patent provides this guidance because a POSA would understand NS5B to be the "target" enzyme or would understand that the modified nucleoside must have "either the natural -OH (hydroxyl) or a mimicking substitute at 2'-down." Appellant's Br. 38, 44. But reliance on a POSA is insufficient to meet the enablement requirement. A patent owner is "required to provide an enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve

as a substitute for the missing information in the specification." *ALZA*, 603 F.3d at 941. Even if we credit Idenix's position that a POSA would look for compounds that would "target" NS5B, the specification fails to provide an enabling disclosure. It is not enough to identify a "target" to be the subject of future testing. A specification that requires a POSA to "engage in an iterative, trial-and-error process to practice the claimed invention" does not provide an enabling disclosure. *Id.*

It is true that the specification contains some data showing working examples of 2'-methyl-up nucleosides with efficacy against HCV. *See* '597 patent col. 139 l. 61–col. 142 l. 57. As discussed, however, the specification alone encompasses tens if not hundreds of thousands of "preferred" 2'-methyl-up nucleosides that would need to be tested for efficacy against HCV. In the face of that broad disclosure, four examples on a single sugar are insufficient to support enablement. Where, as here, working examples are present but are "very narrow, despite the wide breadth of the claims at issue," this factor weighs against enablement. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999); s*ee Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (working example that was "insufficient to enable the breadth of the claims here, especially in light of the unpredictability of the art" did not support enablement).

Because the '597 patent fails to provide meaningful guidance as to which 2'-methyl-up nucleosides are or are not effective against HCV, and because the only working examples provided are exceedingly narrow relative to the claim scope, these two factors weigh in favor of non-enablement.

D

Based on the testimony presented at trial, a reasonable jury could only have concluded that the use of modified nucleosides to treat HCV was an unpredictable art. Gilead's

experts testified at trial that the art was "highly unpredictable" because "in the nucleoside area . . . the smallest change can have a dramatic effect not only on the activity of that compound but on the toxicity of the compound. So nothing is predictable." J.A. 37547.

Idenix's experts also testified at trial that the field was new and unpredictable. On cross-examination, Idenix's expert admitted that at the time the '597 patent was invented, the field of "modified nucleosides activity for HCV" was "in its infancy." J.A. 37736. He also admitted that, even as late as 2012, it was "unpredictable to make a compound and determine whether or not it is active" against HCV. J.A. 37736–37. Another of Idenix's witnesses confirmed that "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it." J.A. 37441.

In light of both parties' testimony that the art was unpredictable, this factor could only weigh in favor of non-enablement. *See In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

E

For largely the same reasons discussed with respect to the quantity of experimentation factor, we conclude that the scope of the claims could only support a finding of non-enablement. On appeal, Idenix makes two arguments specifically directed to this factor. Neither is persuasive.

First, Idenix argues that "[w]hen required to take all of the claim limitations into account, Gilead's witnesses described the claims as embracing only a 'small' number of compounds." Appellant's Br. 46. This analysis is backwards. Gilead's expert testified that, in order for the '597 patent to teach which 2'-methyl-up nucleosides effectively

treat HCV, the patent would need to detail "how to get from a large number [of candidate compounds] to a relatively speaking small number [of effective compounds]." J.A. 37546–47. In other words, the '597 patent leaves a POSA searching for a needle in a haystack to determine which of the "large number" of 2'-methyl-up nucleosides falls into the "small" group of candidates that effectively treats HCV. The size disparity between those two groups requires significant experimentation, which weighs against enablement, not for it.[8]

Second, Idenix argues that the claim is not broad because "evidence showed that the POSA, with common sense, the claims, and the specification as guidance, would focus on a narrow set of candidates." Appellant's Br. 46. This factor, however, considers the scope of the claim as written, not just the subset of the claim that a POSA might practice. Idenix does not, and cannot, argue that the scope of the claim is actually limited to this narrow set of candidates. "[A]s a matter of law, NS5B activity is ***not*** a claim limitation." JMOL Opinion, at *26 (emphasis in original). We therefore conclude that the breadth of the claims weighs in favor of non-enablement.

F

Weighing each of these factors, we conclude as a matter of law that the '597 patent is invalid for lack of enablement. As described above, a reasonable jury could only have found that at least many, many thousands of 2'-methyl-up nucleosides meet the structural limitations of claim 1, not all of which are effective to treat HCV. Due to the

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[8] Although not necessary to our decision, we also note that this "small number" argument is inconsistent with Idenix's claim at oral argument that the jury implicitly found that *all* 2'-methyl-up nucleosides are effective to treat HCV. Oral Arg. at 6:07–18.

unpredictability of the art, and as admitted by Idenix, each of these compounds would need to be screened in order to know whether or not they are effective against HCV. Moreover, a significant number of candidate 2'-methyl-up nucleosides would need to be synthesized before they could be screened, which increases at least the quantity of experimentation required, even if the synthesis was routine. Although the level of skill in the art is high, the '597 patent does not provide enough meaningful guidance or working examples, across the full scope of the claim, to allow a POSA to determine which 2'-methyl-up nucleosides would or would not be effective against HCV without extensive screening. The immense breadth of screening required to determine which 2'-methyl-up nucleosides are effective against HCV can only be described as undue experimentation.

Our decision in *Wyeth and Cordis Corp. v. Abbott Laboratories* compels this conclusion, and as the district court correctly acknowledged, the similarities between that case and this one are striking. In *Wyeth*, as here, we considered a claim that encompassed "millions of compounds made by varying the substituent groups," while only a "significantly smaller" subset of those compounds would have the claimed "functional effects." 720 F.3d at 1384. We then credited the patent owner's argument that, based on the knowledge of a POSA, the number of candidate compounds to be tested could be as little as "tens of thousands." *Id.* at 1384–85. In both cases, scientific testimony confirmed that practicing the full scope of the claims would require synthesizing and screening tens of thousands of candidate compounds for the claimed efficacy. *Compare id.* at 1385 (Wyeth scientist testifying "until you test [compounds], you can't really tell whether they work or not"), *with* J.A. 37441 (Idenix scientist testifying "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it").

Notwithstanding the fact that screening an individual compound for effectiveness was considered "routine," we concluded as a matter of law in *Wyeth* that the claim was not enabled because there were "at least tens of thousands of candidate compounds" and "it would be necessary to first synthesize and then screen *each* candidate compound." *Id.* at 1385–86. As we explicitly stated: "The remaining question is whether having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation. We hold that it does." *Id.* at 1385. That principle controls here. A reasonable jury could only have concluded that there were at least many, many thousands of candidate compounds, many of which would require synthesis and each of which would require screening. That constitutes undue experimentation.

We are not persuaded by Idenix's attempts to distinguish *Wyeth* based on the state of the arts of screening and synthesis in 1992, when the *Wyeth* patent application was filed, as compared to 2000, when Idenix's first application was filed. Our decision in *Wyeth*, and our decision here, rests on the "limits on permissible experimentation," not on the relative time that the experimentation would take. *Id.* at 1386. We found the patent in *Wyeth* not enabled even while "putting the challenges of synthesis aside," and accepting as true that screening was "routine[]." *Id.* at 1384, 1386. Where, as here, "practicing the full scope of the claims would have required excessive experimentation, even if routine," the patent is invalid for lack of enablement. *Id.* at 1384.

IV

We separately address the district court's denial of JMOL on the issue of written description. The Patent Act contains a written description requirement distinct from the enablement requirement. 35 U.S.C. § 112; *see Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc). To fulfill the written description

requirement, a patent owner "must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (citation omitted) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991)). That test "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351.

The question in this case is whether the '597 patent demonstrates that the inventor was in possession of those 2'-methyl-up nucleosides that fall within the boundaries of the claim (i.e., are effective against HCV), but are not encompassed by the explicit formulas or examples provided in the specification. The parties focus in particular on whether the specification demonstrates possession of the 2'-methyl-up 2'-fluoro-down nucleosides that are the basis for Gilead's accused product.

There is no dispute that neither the '597 patent nor any of its predecessor applications discloses a 2'-methyl-up 2'-fluoro-down nucleoside, including in any formulas or examples. *See* J.A. 37102–03 (admission of Idenix's inventor). Nor is there any dispute as to why. Idenix "only came up with the methyl up fluoro down embodiment a year or so after the application was filed." *See* J.A. 25562 (admission of Idenix's counsel). Idenix argues instead that its claims are directed to the entire genus of 2'-methyl-up compounds for treating HCV, and are enabled by the disclosure of a number of examples, without needing to disclose each species of nucleoside. *See* Reply Br. 31–32.

Idenix is correct that generally a genus can be sufficiently disclosed by "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one

of skill in the art can visualize or recognize the members of the genus." *Ariad*, 598 F.3d at 1350 (internal quotation marks omitted). We have alternatively described this inquiry as "looking for blaze marks which single out particular trees" in a forest, rather than simply "pointing to trees." *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) (quoting *In re Ruschig*, 379 F.2d 990, 994–95 (CCPA 1967)).

In this case, we hold that the '597 patent is invalid for lack of written description, as it fails to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV. The patent provides eighteen position-by-position formulas describing "principal embodiments" of compounds that may treat HCV. *See generally* '597 patent col. 5 l. 29–col. 13 l. 42. However, other than generic language regarding "pharmaceutically acceptable salts and prodrugs thereof" (a category not at issue here), the specification provides no indication that any nucleosides outside of those disclosed in its formulas could be effective to treat HCV—much less any indication as to *which* of those undisclosed nucleosides would be effective. *See id.* at col. 15 l. 51–col. 16 l. 10. "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to distinguish it from other materials." *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363 (Fed. Cir. 2011) (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). The '597 patent provides adequate written description for the compounds within its formulas. The specification, however, provides no method of distinguishing effective from ineffective compounds for the compounds reaching beyond the formulas disclosed in the '597 patent.

Idenix argues that it provides "abundant traditional blazemarks for the claims—working examples, formulas,

data, synthesis routes, and the target." Reply Br. 32. Each of these suffer from the same flaw. They provide lists or examples of supposedly effective nucleosides, but do not explain what makes them effective, or why. As a result, a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result. In the absence of that guidance, the listed examples and formulas cannot provide adequate written description support for undisclosed nucleosides that also happens to treat HCV. The written description requirement specifically defends against such attempts to "cover any compound later actually invented and determined to fall within the claim's functional boundaries." *See Ariad*, 598 F.3d at 1353.

We are mindful of *Ariad*'s caution that written description does not require "a nucleotide-by-nucleotide recitation of the entire genus." *Id.* at 1352. The purpose of that rule is to allow relatively few representative examples or formulas to support a claim on a structurally similar genus. *See id.* It does not extend to this case, where the specification lists tens or hundreds of thousands of possible nucleosides, substituent-by-substituent, with dozens of distinct stereochemical structures, and yet the compound in question is conspicuously absent.

The absence of 2'-fluoro-down is indeed conspicuous. Seven of the provided formulas permit 2'-methyl-up. *See, e.g.*, '597 patent col. 6 ll. 5–20 (Formula II), col. 8 ll. 5–20 (Formula V), col. 10 ll. 5–47 (Formulas X and XI), col. 11 l. 42–col. 12 l. 17 (Formula XVI), col. 12 ll. 23–54 (Formula XVII), col. 13 ll. 5–41 (Formula XVIII). All seven formulas explicitly list fluorine as a possibility at other positions, including 2'-up. *See, e.g.*, *id.* at col. 10 ll. 42–47 (listing "fluoro" at 2'-up). Yet not one of them includes fluorine at 2'-down, despite each listing more than a dozen possible substituents at that position. This is true even though the formulas include every other recited halogen at both positions. *Compare* '597 patent col. 8 ll. 48–54 (listing "chloro,

bromo, fluoro, iodo" at 2'-up), *with* col. 8 ll. 55–61 (listing "chlorine, bromine, iodine," but not fluorine, at 2'-down).

Further, to the extent Idenix argues that, although not disclosed, a POSA would have known to include fluorine at 2'-down based on its similarities to other halogens, that is insufficient for written description. "[A] description that merely renders the invention obvious does not satisfy" the written description requirement. *Ariad*, 598 F.3d at 1352.

We therefore disagree with Idenix's characterization that "the specification plainly embraces the use of the [2'-fluoro-down] embodiment." Reply Br. 34. In light of the conspicuous absence of that compound, a POSA would not "visualize or recognize the members of the genus" as including 2'-fluoro-down, and the specification could not demonstrate to a POSA that the inventor had possession of that embodiment at the time of filing. *Ariad*, 598 F.3d at 1350.

V

For the foregoing reasons, we affirm the district court's grant of judgment as a matter of law that the '597 patent is invalid for lack of enablement. We reverse the district court's denial of judgment as a matter of law for failure to meet the written description requirement and hold that the '597 patent is invalid for lack of written description as well.

AFFIRMED-IN-PART AND REVERSED-IN-PART

COSTS

Costs to appellee.

United States Court of Appeals for the Federal Circuit

IDENIX PHARMACEUTICALS LLC, UNIVERSITA DEGLI STUDI DI CAGLIARI,
Plaintiffs-Appellants

v.

GILEAD SCIENCES INC.,
Defendant-Appellee

2018-1691

Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-00846-LPS, Chief Judge Leonard P. Stark.

NEWMAN, *Circuit Judge*, dissenting.

I respectfully dissent. The court errs in holding that the specific narrow claims of the '597 patent are invalid. The large number of unclaimed chemical variants in the specification are not described, not synthesized, and not tested for antiviral activity. It is incorrect to include these variants in the claims and then to invalidate the claims because these variants are not described and not enabled.

The panel majority, overturning the jury verdict, finds the '597 claims invalid on the grounds of non-enablement and inadequate description. The majority finds that there are "billions and billions" of possible nucleosides in the omnibus specification. On this reasoning, the majority finds

invalid the narrow claims of the '597 patent. However, a reasonable jury could have understood the claims as directed to the nucleosides that are specifically described and that are shown to have the claimed antiviral activity. A reasonable jury could have credited the evidence that the '597 claims are for these specific compounds, not the "billions and billions" of unsynthesized and unevaluated variants in the specification. It is not disputed that the specific claimed compounds meet the requirements of 35 U.S.C. § 112. The jury verdict of validity must be viewed in light of the evidence and argument before the jury.

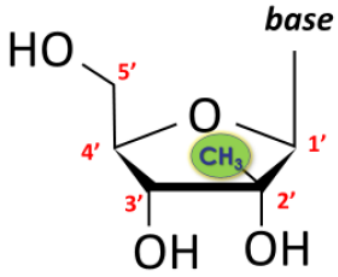
The majority's holding that validity under section 112 is determined based on whether unclaimed subject matter is described and enabled, provides a new path of uncertainty and unreliability of the patent grant. I respectfully dissent.

I

I write in concern for the majority's flawed theory of section 112, whereby the court requires description and enablement of the unclaimed and unsupported subject matter, in order to sustain validity of claims to the supported subject matter. A reasonable jury could have applied the jury instructions, in light of the patent document and the testimony of witnesses, to understand that the claims are for the subject matter that is produced and described and evaluated for antiviral activity. On the correct claim construction, a reasonable jury could have found the claimed subject matter to be described and enabled.

A reasonable jury could have understood that subject matter that is unclaimed is irrelevant to validity under section 112. With all respect to my colleagues, they err in holding that because "billions and billions" of nucleosides are within the specification but not characterized and not evaluated, the claims to the products that are synthesized and shown to have antiviral activity are invalid as "indefinite."

The jury could have found, as witnesses testified, that the claims are directed to the nucleosides that are synthesized as shown in the '597 specification, and shown to have antiviral efficacy. This is a narrow class of nucleosides, pictured as set forth in the briefs and in the majority's opinion:



Idenix Br. 8; Gilead Br. 8; Maj. Op. at 5.

The '597 specification is an omnibus disclosure of eighteen broad "Formulas" of nucleosides—variants that are untested, uncharacterized, and unclaimed. In contrast, only the above molecule is included in the patent Figures that report antiviral data. The specification describes Figures 2 and 3 as follows:

> FIG. **2** is a line graph of the pharmacokinetics (plasma concentrations) of ß-D-2'-CH_3-riboG administered to six Cynomolgus Monkeys over time after administration.
>
> FIGS. **3***a* and **3***b* are line graphs of the pharmacokinetics (plasma concentrations) of ß-D-2'-CH_3-riboG administered to Cynomolgus Monkeys either intravenously (**3***a*) or orally (**3***b*) over time after administration.

'597 patent, col. 15, ll. 31–38. Figure 1, captioned "Chemical Structure of Illustrative Nucleosides," presents the structures of eight nucleosides and two comparative compounds. '597 patent, col. 15, ll. 27–30 ("FIAU and Ribavirin, which are used as comparative examples"). All eight

nucleosides have the three OH groups in the positions and stereochemistry pictured above, and six of the eight structures in Figure 1 also have a methyl group in the 2'-up position as required by all the claims.

The jury was told by Dr. Meier, an expert witness for Idenix, that for all of the 2'-methyl-up nucleosides in Figure 1, "all of the compounds have hydroxide at the 2' down position." J.A. 37673 at 1859:25–1860:2. Dr. Secrist, an expert witness for Gilead, testified that the first four compounds in Figure 1 are ß-D-2'-methyl-ribofuranosyl nucleosides, stating "[a]ll of them have a 2' up methyl and a 2' down hydroxyl, yes, and they are ribonucleoside." J.A. 37638 at 1721:8–11.

My colleagues err in ruling that the claims cover "billions" of variants. The '597 specification recites a very large number of substituents for nucleosides that are not synthesized, not characterized, not evaluated, and not included in the claims. Some of these variants have been claimed in other patents and applications.[1] However, they are not claimed in the '597 patent. My colleagues err in holding that because other substituents and modifications

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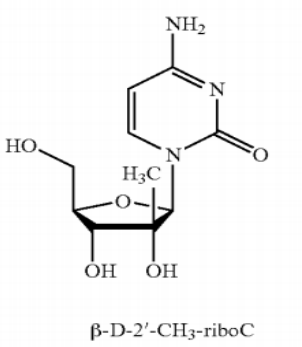
[1] At least nine additional patents and applications are reported to claim priority from this Provisional Application No. 60/206,585, *viz.* Patent No. 6,914,054 (claiming Formulas V, X, XI, XVI, XVII, and XVIII); Patent No. 7,169,766 (claiming Formula XVII); Application No. 10/602,142 (claiming Formulas X, XI, and XVII); Patent No. 7,157,441 (claiming Formulas II, X, XI, XVII); Patent No. 8,299,038 (claiming Formulas II and V); Application No. 13/623,674 (claiming Formulas X, XI, XVI, XVII, and XVIII); Patent No. 10,363,265 (claiming Formulas V and X); Application No. 13/953,687 (claiming Formula XI); Application No. 16/440,659. *See* USPTO's PAIR database at http://portal.uspto.gov/pair/PublicPair, tab "Continuity Data."

are mentioned in the specification, claims that do not include such variants are invalid on grounds of indefiniteness and lack of written description.

The broadest claim of the '597 patent is claim 1:

> 1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine ß-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

'597 patent, col. 142, ll. 63–67. This nucleoside with pyrimidine base is pictured and labeled in the specification as follows:



β-D-2′-CH_3-riboC

'597 patent, col. 142, ll. 43–55. The specification provides pharmacologic data for the ß-D-2'-methyl-ribofuranosyl nucleosides of the claimed structure. The narrow scope exemplified in the specification cannot be reconciled with the majority's count of "billions and billions," Maj. Op. at 9; or "hundreds of millions," *id.*; or even "many, many thousands," *id.* at 12, of nucleosides covered by the claims.

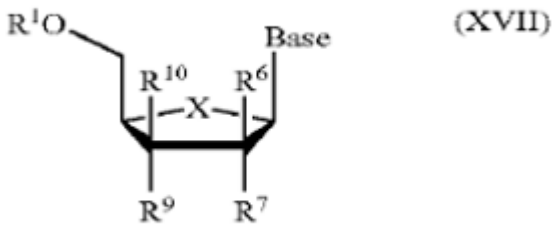
The jury was instructed that the claims define a patent's scope:

> The claims are important because it is the words of the claims that define what a patent covers. The claims are intended to define, in words, the

> boundaries of the invention that constitute the patent owner's property rights. The figures and text in the rest of the patent provide a description and/or examples of the invention and provide a context for the claims, but it is the claims that define the breadth of the patent's coverage. Each of the asserted claims must be considered individually.

J.A. 169; J.A. 37800 at 2068:17–25 (instructing the jury).

The panel majority discards this instruction, and reproduces in the majority opinion portions of the specification that relate to the other "Formulas" that are pictured in the specification and directed to other nucleosides, some of which are the subject of continuation patents and applications. *See* n.1, *ante*. For example, the majority presents the specification structure designated Formula XVII, which depicts, with "R" and "X" designations, a large number of substituents of the molecule:



(XVII)

Maj. Op. at 10–11 (citing '597 patent, col. 12, ll. 20–67). The majority states that the variants for Formula XVII are "more than 7,000." *Id.* at 12. However, a reasonable jury could have understood, as witnesses for both sides testified, that the only variants synthesized and evaluated in the '597 patent have the structure where R^1 is H, R^9 is OH, R^{10} is H, R^7 is OH, R^6 is CH_3, and X is oxygen.

The '597 patent was the subject of expert testimony throughout the two-week jury trial. The patent was given to the jury; *see* J.A. 170 ("[R]efer to the copy of the '597 patent that you have been given."). Following is a sampling of the expert testimony:

- Q. Is the difference between DNA and RNA at 2' down, so OH in RNA, the H in DNA, is that important to a nucleoside chemist in 2000-2001? A. Oh, yes. It is a critical distinction, of course. J.A. 37543 at 1568:9–12.
- Q. Now, you have depicted the treatment with an OH down at 2'. Is that correct? A. Yes. Q. Why did you do that? A. Well, it's – number one, you would expect, when you're making something – this is in the 2001 time frame, you would expect modified nucleotides to have that OH down because you want to be accepted by the machinery that makes that RNA virus. So you want to have that 2- down. J.A. 37544 at 1571:1–10.
- Q. [Discussing a 1998 publication concerning the enzymes] If you look at the end of the paragraph, it concludes with the statement that "These results indicate that the HCV enzyme has a strict specificity for ribonucleoside 5' triphosphates and requires the 2' and 3'-OH groups." . . . What does that mean with respect to this 2' position you and I have just been talking about? A. Well, as I have always maintained, the entire molecule, when you are making a drug, is absolutely critical. However, in the case of doing something for RNA, then having this 2' prime, for the reasons I talked about earlier, that's what the enzymes use, is really important. J.A. 37545 at 1574:16–1575:2.

- Q. In the patent, did you see, after reading it, any data on any other nucleoside that had something different at 2' down than the OH known as hydroxyl? A. No. J.A. 37548 at 1588:18–21.
- Q. What did these examples teach a skilled person to put at the 2' down position in a nucleoside? A. Well, if you are thinking about effective treatment of HCV, at best they teach that you would put an OH down at the 2' along with a methyl up at the 2 prime. J.A. 37548 at 1588:22–1589:1.
- Q. And is that teaching, OH down at 2', is that consistent or inconsistent with the conventional wisdom of nucleoside chemists at the time? A. Well, speaking as a nucleoside chemist at the time, I would have expected and certainly not been surprised by compounds identified that had 2' down hydroxyls. J.A. 37548 at 1589:4–9.
- Q. We talked about this, but . . . is there any antiviral data to guide the person of skill amongst the possibilities covered by that 2'-Beta-D-methyl-ribofuranosyl nucleoside? A. No. We heard about it before but there is no antiviral data in this patent application. J.A. 37549–50 at 1593:20–1594:1.
- Q. And even considering that other data, does that cover a lot of compounds or only a few? A. Well, it only covers the four compounds and they all have the 2' down OH only at this critical spot, 2' down. J.A. 37550 at 1594:2–5.
- Q. Let's turn to the making of the compound. What kind of guidance does the patent provide and what kind of compounds are actually – or

the patent teaches you can actually make? A. Well, it gives, I'll say, standard literature ways to make nucleosides that have 2' up methyl and a 2' or maybe even a 2' up alkyl and a 2' down OH. J.A. 37550 at 1594:6–12.

- Q. [Displaying the '597 patent] What are we looking at here, Dr. Secrist, at DDX-721, which excerpts the patent at column 48, lines 30 to page [sic] 49, line 5? A. This is one of two general schemes that are in the patent, and I won't go through it other than to note that you take a starting material, that you go through a whole series of steps, and you end up with a nucleoside with a down OH. J.A. 37550 at 1594:13–21.
- Q. And a 2'-methyl up? A. A 2'-methyl, or as you can sigh [sic] in ours, it could be another group up. J.A. 37550 at 1595:16–18.
- Q. What compound does the patent show being made in relation to the 2' position? A. Okay. It shows only compounds that have a 2' down hydroxyl group. J.A. 37550 at 1595:12–15.
- Q. Are there any other synthetic schemes, any other schemes in the patent that show something different at 2' down? A. No, just OH. J.A. 37550 at 1595:19–22.
- Q. Does the patent show any of these compounds being made at R7 other than 2' OH down? A. No. J.A. 37551 at 1598:10–12.
- Q. So Dr. De Francesco, we were just talking about your 2003 paper. We were talking about the phrase . . . Beta-D 2' methyl ribofuranosyl guanosine, and I think where we left off was that you were confirming that that phrasing describes the structure . . . that's a methyl up

> at the 2' position, OH or hydroxy down at the 2' and 3' position? A. Right. Correct. J.A. 37755 at 2001:19–2002:3.

There's much more, as the jury was informed concerning the chemical structure, the specification, and the claims. The verdict form was explicit as to the asserted claims and the burden of proof:

> [1] Has Gilead proven by clear and convincing evidence that each of the asserted claims of the '597 patent is invalid because the specification of the '597 patent does not enable the asserted claims?
>
> [2] Has Gilead proven by clear and convincing evidence that each of the asserted claims of the '597 patent is invalid because the specification of the '597 patent does not contain an adequate written description of the asserted claims?

J.A. 143. The jury answered "No" to both questions. *Id.*

The panel majority now discards the jury verdict, stating "the jury was not free to adopt a number lower than the many, many thousands of configurations identified as 'principal embodiment[s]' in the patent itself." Maj. Op. at 12 (alteration in original). However, the jury was not free to adopt an incorrect view of the patent, for almost all of the embodiments that the specification calls "principal embodiments" are for Formulas for which no synthesis and no evaluation data are provided in the '597 specification.

The panel majority makes no mention of the relation of the '597 claims to the Figures, the examples, and the data in the specification, holding only that the claims are invalid based on "billions and billions" of unclaimed nucleosides. Gilead's expert Dr. Secrist testified that the preferred subembodiments of Formula XVII "ends up with a total of five compounds":

> Q. To be fair, the patent does boil these formulas down a little bit down into something called preferred embodiments. Is that true? A. Absolutely, it does.
>
> Q. Can you explain, it is a term we haven't heard before, can you explain to the jury what your understanding of a preferred embodiment is? A. Well, you take—I will do my best. If you have this many compounds that you are starting with, a preferred embodiment would narrow it down by some means, usually by looking at data, to this many, in a more preferred embodiment similarly by some means, usually data would get down to this number of compounds. So you would go from here to here with preferred embodiments, usually based on seeing the data for compounds that are in these embodiments. . . .
>
> Q. If we go to [the '597 patent]. What are we looking at here, Dr. Secrist, from Column 32 of the patent, lines 42 to 59? A. On the right is the same structures, Roman Numeral XVII that we have already seen. Now we are looking at what's up and what's down at the 2' position. . . . I have suggested it is an important position. It is. What they show is a methyl up, you can see it, R6 is methyl in all cases and a hydroxyl down in all cases. This ends up with a total of five compounds.

J.A. 37554 at 1612:4–1613:7.

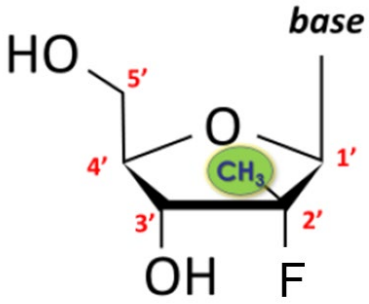
A patent specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 para. 1. It was undisputed that the '597 specification did not describe and enable products other than those whose synthesis and antiviral properties were shown in the

specification, all of which had the narrow formula of three OH groups and a CH_3 group as pictured. A reasonable jury could have so viewed the claims. "Courts are not free to reweigh the evidence and set aside the jury verdict merely because the jury could have drawn different inferences or conclusions or because judges feel that other results are more reasonable." *Tennant v. Peoria & P.U. Ry. Co.*, 321 U.S. 29, 35 (1944).

Based on the evidence, a reasonable jury could have found that the claims are directed to the subject matter that was described and evaluated. "Our appellate role ends when there is shown to be substantial evidence, on the record as a whole, as could have been accepted by a reasonable jury as probative of the issue." *Nat'l Presto Indus., Inc. v. West Bend Co.*, 76 F.3d 1185, 1192 (Fed. Cir. 1996). My colleagues err in holding that the '597 claims are invalid unless the billons or millions or thousands of variants are synthesized and shown to have antiviral activity. The evidence could reasonably support a jury finding that the claims are of the scope that is described and enabled in conformity with section 112. From my colleagues' contrary ruling, I respectfully dissent.

II

The basis of this litigation is Idenix's complaint that the '597 patent is infringed by the Gilead product sofosbuvir, which has a fluorine substituent in the 2'-down position, as follows:



The issue in litigation was whether this product infringes the '597 claims. Gilead presented extensive testimony and argument on this question. For example, there was testimony that this product could not be made by the procedures in the '597 specification. There was testimony that an Idenix scientist had tried and failed to synthesize this fluorine-containing molecule. J.A. 37402–03 at 1178:2–1179:20. A witness testified that attaching fluorine to a nucleoside is "very tricky," for "it could lead to compounds that explode." J.A. 37279 at 836:12–837:1. There was testimony that it was known that 2'-F nucleosides were toxic. J.A. 37196 at 696:6–10, J.A. 37286 at 866:5–14, J.A. 37327 at 1030:7–22. There was testimony about stereochemical doubts that this molecule could be produced. J.A. 37314 at 976:22–977:13, J.A. 37319 at 998:6–999:23.

It is pointed out that fluorine is conspicuously omitted from the list of halogen substituents at 2'-down in several of the general "Formulas" in the '597 specification. Gilead Br. at 68–69 (citing '597 patent, col. 10, ll. 42–55, col. 12, ll. 5–12, col. 12, ll. 55–61). It is pointed out that Idenix lost an interference contest on this specific molecule. Gilead Br. at 1 (citing *Storer v. Clark*, 860 F.3d 1340 (Fed. Cir. 2017)).

The panel majority states that this aspect was "not advanced by Idenix at trial or before us." Maj. Op. at 7–8 n.3. However, Gilead did advance this aspect at trial, and argues it on this appeal. At the trial Gilead presented evidence with respect to the 2'-down fluorine substituent, as I have outlined, and on appeal Gilead devotes a substantial portion of its brief to the argument that its fluorinated compound is not within the scope of correctly construed claims. The issue was not waived, although the Supreme Court has recognized that even issues that were waived may be considered on appeal. The Court has explained:

> Nor did prudence oblige the Court of Appeals to treat the unasserted argument . . . as having been waived. . . . [A] court may consider an issue "antecedent to . . . and ultimately dispositive of" the dispute before it, even an issue the parties fail to identify and brief. . . . [A] court "need not render judgment on the basis of a rule of law . . . simply because the parties agree upon it."

U.S. Nat'l Bank of Or. v. Indep. Ins. Agents of Am., 508 U.S. 439, 447 (1993) (quoting *Arcadia v. Ohio Power Co.*, 498 U.S. 73, 77 (1990) and *United States v. Burke*, 504 U.S. 229, 246 (1992) (Scalia, J., concurring in judgment)).

The judicial responsibility and authority are to assure that the correct law is applied. Contrary to my colleagues' position, the Court admonishes that:

> Rules of practice and procedure are devised to promote the ends of justice, not to defeat them. A rigid and undeviating judicially declared practice under which courts of review would invariably and under all circumstances decline to consider all questions which had not previously been specifically urged would be out of harmony with this policy. Orderly rules of procedure do not require sacrifice of the rules of fundamental justice.

Hormel v. Helvering, 312 U.S. 552, 557 (1941); *see Singleton v. Wulff*, 428 U.S. 106, 121 (1976) ("The matter of what questions may be taken up and resolved for the first time on appeal is one left primarily to the discretion of the courts of appeals, to be exercised on the facts of individual cases. We announce no general rule.").

The Federal Circuit has so recognized. *See Wilson v. Principi*, 391 F.3d 1203, 1211 (Fed. Cir. 2004) ("The Court stated that such instances should be based on 'particular circumstances which will prompt a reviewing or appellate court, where injustice might otherwise result, to consider

questions of law which were neither pressed nor passed upon . . . below.' The matter is one left largely to the discretion of the court of appeals." (quoting *Hormel*, 312 U.S. at 557)). On appeal, our responsibility is to the law, and just conduct of the appeal.

There was substantial evidence that Gilead's fluorinated product is not within the scope of the claims as they reasonably could have been viewed by the jury. The jury verdict of validity under section 112 is in accordance with law and supported by substantial evidence. I would decide this appeal on the ground that the claims, correctly construed, are valid and not infringed. From my colleagues' contrary rulings, I respectfully dissent.

CERTIFICATE OF COMPLIANCE

1. This petition complies with the type-volume limitation of Federal Rule of Appellate Procedure 35(b)(2)(A): This petition contains 3,895 words, excluding the exempted parts of the petition.

2. This petition complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6): This petition has been prepared in a proportionally spaced typeface using Microsoft Word 2018 in 14-point Times New Roman.

Dated: January 15, 2020

/s/ Lisa L. Furby
Lisa L. Furby
Counsel for Appellants

CERTIFICATE OF SERVICE

I hereby certify that on January 15, 2020, I served a copy of the foregoing on all counsel of record by CM/ECF.

Dated: January 15, 2020

/s/ Lisa L. Furby
Lisa. L. Furby
Counsel for Appellants