United States Court of Appeals for the Federal Circuit

BRISTOL-MYERS SQUIBB COMPANY,
Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Appellee.

2013-1306

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0805, Magistrate Judge Christopher J. Burke

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ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

WILLIAM F. LEE, Wilmer Cutler Pickering Hale and Dorr, LLP, of Boston, Massachusetts, filed a petition for panel rehearing and rehearing en banc for plaintiff-appellant. With him on the petition were LAUREN B. FLETCHER and ANDREW J. DANFORD, of Boston, Massachusetts, and AMY K. WIGMORE and THOMAS G. SAUNDERS, of Washington, DC. Of counsel on the petition were PAUL H. BERGHOFF, ALISON J. BALDWIN, and JOSHUA RICH, McDonnell Boehnen Hulbert & Berghoff LLP, of Chicago, Illinois.

GEORGE C. LOMBARDI, Winston & Strawn LLP, of Chicago, Illinois, filed a response for defendant-appellee.

With him on the response were LYNN MACDONALD ULRICH, IVAN M. POULLAOS, JULIA MANO JOHNSON, and WILLIAM P. FERRANTI.

JONATHAN E. SINGER, Fish & Richardson P.C., of Minneapolis, Minnesota, for amicus curiae Biotechnology Industry Organization. With him on the brief was CRAIG E. COUNTRYMAN, of San Diego, California.

HOWARD W. LEVINE, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Washington, DC, for amicus curiae Bay Area Bioscience Association. With him on the brief was JENNIFER S. SWAN, of Palo Alto, California.

ROY F. WALDRON, Pfizer Inc., of New York, New York, for amicus curiae Pfizer Inc. With him on the brief were JEFFREY J. OELKE, LESLIE MORIOKA, and ROBERT E. COUNIHAN, White & Case LLP, of New York, New York.

STEVEN P. CALTRIDER, Eli Lilly and Company, of Indianapolis, Indiana, for amicus curiae Eli Lilly and Company.

CARTER G. PHILLIPS, Sidley Austin LLP, of Washington, DC, for amicus curiae Pharmaceutical Research and Manufacturers of America. With him on the brief were JEFFREY P. KUSHAN, RYAN C. MORRIS, and JAMES A. HIGH, JR.

ROBERT M. ISACKSON, Orrick, Herrington & Sutcliffe LLP, of New York, New York, for amicus curiae Intellectual Property Owners Association. With him on the brief were ELIZABETH A. HOWARD and T. VANN PEARCE. Of counsel on the brief were PHILIP S. JOHNSON and KEVIN H. RHODES, Intellectual Property Owners Association, of Washington, DC. Of counsel was HERBERT C. WAMSLEY, JR.

NICHOLAS G. BARZOUKAS, Baker Botts L.L.P., of Houston, Texas, for amicus curiae Merck Sharp & Dohme

Corp. With him on the brief was JOSHUA DAVIS. Of counsel on the brief were WILLIAM KROVATIN and GERARD M. DEVLIN, Merck Sharp & Dohme Corp., of Rahway, New Jersey.

Before PROST, *Chief Judge*, NEWMAN, PLAGER[1], LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, and HUGHES, *Circuit Judges*.

DYK, *Circuit Judge*, with whom WALLACH, *Circuit Judge*, joins, concurs in the denial of the petition for rehearing en banc.

O'MALLEY, *Circuit Judge*, concurs in the denial of the petition for rehearing en banc.

NEWMAN, *Circuit Judge*, with whom LOURIE and REYNA, *Circuit Judges*, join, dissents from the denial of the petition for rehearing en banc.

TARANTO, *Circuit Judge*, with whom LOURIE and REYNA, *Circuit Judges*, join, dissents from the denial of the petition for rehearing en banc.

PER CURIAM.

O R D E R

A combined petition for panel rehearing and rehearing en banc was filed by plaintiff-appellant Bristol-Meyers Squibb Company, and a response thereto was invited by the court and filed by defendant-appellee Teva Pharmaceuticals USA, Inc. The petition for rehearing and response were referred to the panel that heard the appeal, and thereafter, the petition for rehearing en banc and response were referred to the circuit judges who are authorized to request a poll of whether to rehear the appeal en banc. A poll was requested, taken, and failed.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) The petition for panel rehearing is denied.

(2) The petition for rehearing en banc is denied.

(3) The mandate of the court will issue on October 27, 2014.

FOR THE COURT

October 20, 2014
Date

/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk of Court

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[1] Circuit Judge Plager participated only in the decision on the petition for panel rehearing.

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DYK, *Circuit Judge*, with whom WALLACH, *Circuit Judge*, joins, concurring in the denial of the petition for rehearing en banc.

This case presents a question of obviousness, in particular whether evidence postdating the invention can be used to establish unexpected results. The panel holds that it cannot be considered in the circumstances of this case. That position is correct. It is mandated by the statute, which provides that an invention is not patentable if it "would have been obvious *before the effective filing date* of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103 (emphasis added).

The patent applicant's discovery of unexpected results at the time of the invention can help to establish that the invention would not have been obvious to another skilled person. But hindsight bias must be avoided in determining obviousness. And under longstanding Supreme Court authority, the pertinent knowledge is that possessed at the time of the invention. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) (focusing on "[w]hen Adams designed his battery" and noting that "[t]he fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams' design was not obvious to those skilled in the art.") (citing *United States v. Adams*, 383 U.S. 39 (1966)); *Ball & Socket Fastener Co. v. Kraetzer*, 150 U.S. 111, 116–17 (1893) (discounting an advantage of a patented invention that "was not originally within the contemplation of the patentee, but is an afterthought"); *see also Genetics Inst., LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1315 (Fed. Cir. 2011) (Dyk, J., dissenting). This decision properly does not allow consideration of post-invention evidence in the circumstances of this case. There is no basis for rehearing en banc.

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O'MALLEY, *Circuit Judge*, concurring in the denial of the petition for rehearing en banc.

I concur in the court's denial of the petition for rehearing en banc. I write to assuage Bristol-Myers Squibb Co.'s ("BMS") and the amici's[1] fears that this panel decision has rewritten the test for obviousness for pharmaceutical patents. In my view, the concerns expressed are unjusti-

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[1] Merck Sharp & Dohme Corp., Intellectual Property Owners Association, Pharmaceutical Research and Manufacturers of America, Eli Lilly & Co., Pfizer Inc., Biotechnology Industry Organization, and Bay Area Bioscience Association (collectively, "the amici").

fied and mischaracterize the opinion. This case does not forge new ground or set down immutable principles. It simply decides that, on the record before it, the district court did not err in finding the asserted claim of the '244 Patent invalid as obvious.

As the panel opinion explains, an invention is unpatentable when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2006).[2] Obviousness is a question of law based on the following underlying factual findings: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claims and the prior art; and (4) objective indicia of nonobviousness, such as commercial success, long-felt but unmet needs, failure of others, and unexpected results. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In this case, the panel affirmed the district court's conclusion that entecavir, BMS's antiviral compound used to treat hepatitis B, was invalid as obvious.[3] The panel found the record supported the selection of 2'-CDG as a lead compound and the conclusion that one of ordinary skill in the art would have been motivated to modify 2'-CDG in such a way to arrive at the patented compound,

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[2] Because this invention was filed before the adoption of the America Invents Act, the prior version of § 103 governs.

[3] Specifically, the district court found that claim 8 of U.S. Patent No. 5,206,244 was invalid as obvious. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 686 (D. Del. 2013).

entecavir. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 975 (Fed. Cir. 2014). The panel then agreed with the district court that, despite some evidence of objective indicia demonstrating non-obviousness, the totality of the evidence supported the conclusion that entecavir was obvious. *Id.* at 979.

In the petition for rehearing en banc and the supporting amicus briefs, BMS and the amici claim that, in reaching its judgment, the panel dramatically altered the jurisprudential landscape governing obviousness claims in pharmaceutical cases. And they predict that dire consequences will flow therefrom. They express concern about (1) the panel's treatment of post-invention evidence regarding the differences between the prior art and the invention, specifically when determining if a skilled artisan would have been motivated to make the claimed compound with a reasonable expectation of success for its therapeutic use; (2) the panel's description of what constitutes an unexpected result in the pharmaceutical context; (3) the party upon whom it placed the burden of proof at certain stages of its obviousness inquiry; and (4) the way in which the panel weighed the evidence of objective indicia of non-obviousness.

BMS and the amici first contend that the panel improperly limits consideration of evidence regarding the properties of the invention and the prior art to those known at the time of the invention. Specifically, BMS and the amici argue the panel forecloses the possibility of reviewing later-discovered differences between the prior art and the claimed invention by requiring these differences to be unexpected "by one of ordinary skill in the art *at the time of the invention*." *Id.* at 977 (emphasis added). BMS and the amici allege that the panel erred by not considering later-discovered unexpected results, and now closes the door to all reference to such evidence. I disagree.

Our case law clearly allows the consideration of later-discovered differences between the prior art and the invention. *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis . . . . That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) ("[E]vidence of unexpected results may be [considered] . . . even if that evidence was obtained after the patent's filing or issue date."); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application."). These differences inform the obviousness analysis and thus can be considered when assessing what was understood by one of skill in the art at the time of the invention and what expectations may have been reasonable.

Like all evidence of objective indicia, the point of considering later-understood evidence regarding the properties of the invention is to guard against hindsight bias by assessing claims of a motivation to combine as of the time of invention *in light of later surprises or developments*. *KSR Int'l Co.*, 550 U.S. at 421; *see Graham*, 383 U.S. at 36; *cf. Sinclair Refining Co. v. Jenkins Petroleum Process Co.*, 289 U.S. 689, 697–98 (1932) ("The law will make the best appraisal that it can, summoning to its services whatever aids it can command [to assess a claimed knowledge base or expectation]. . . . [I]f years have gone by before the evidence is offered[,] [later acquired e]xperience is then available to correct uncertain prophecy. Here is a book of wisdom that courts may not neglect.

We find no rule of law that sets a clasp upon its pages and forbids us to look within."). The panel opinion could not rewrite this precedent even if it wanted to; in this case, I see no evidence it sought to do so.

The line of the opinion to which BMS and the amici refer simply notes that the inquiry into what one of skill in the art understood and reasonably expected must be fixed as of the time of the invention. It does *not* say only properties of the invention known at the time of the invention can be considered for purposes of informing that inquiry. Indeed, as we have said repeatedly over the years, post-issuance evidence regarding objective indicia of non-obviousness may often be the most probative and cogent evidence in the record. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). This is especially true where the post-issuance evidence relates to unexpected results. *See Sanofi-Aventis*, 748 F.3d at 1360.

Apparently recognizing that the panel opinion does not expressly purport to change the law, BMS and the amici argue that, by adopting the district court's finding that 2'-CDG was considered safe and non-toxic at the time of the invention, despite evidence that it was later determined to be toxic, the panel implicitly condoned the exclusion of evidence regarding later-discovered properties, in this and future cases. There is a distinction between limiting the obviousness inquiry to pre-invention evidence and finding post-invention evidence unpersuasive, however. *See Allergan Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) ("We agree with the court's finding that this result was unexpected. However, we do not find that these unexpected results are sufficient to outweigh the other evidence of obviousness.").

What the district court found was that the later evidence of 2'-CDG's toxicity was insufficient to overcome the strong evidence that researchers at the time had a motivation to start with 2'-CDG as the lead compound and

modify it in such a way as to make entecavir. The court then cited a host of evidence in the record to support that conclusion. BMS and the amici say that the trial court's conclusion cannot have been correct because 2'-CDG was later shown to be toxic. They argue that no medicinal chemist could have had a reasonable expectation of success from use of 2'-CDG as a lead compound because they could not have known if any modification to it would be safe for human use.

As the district court pointed out, BMS did not question the reasonableness of a skilled artisan's expectation on these grounds until its reply brief before the trial court and, thus, arguably waived that argument. *Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 674 n.36. And, the district court rejected the merits of BMS's argument, finding that the level of 2'-CDG's cytotoxicity was not known at the time of the invention and that tentative concerns about the toxicity did not stop researchers from using 2'-CDG as a starting point. As the district court said, "the best indication that any such tentative references to possible toxicity did not stop the medicinal chemist from selecting 2'-CDG as a lead compound in the late 1980s and 1990, in light of its positive benefits, is the fact that researchers were *actually treating and using* 2'-CDG as a lead compound during the relevant time period." *Id.* at 662. Indeed, BMS's own expert, Dr. Bud Tennant, testified that, during his experiments investigating the effects of 2'-CDG against the woodchuck hepatitis virus—which occurred after entecavir's invention—he was surprised to find 2'-CDG was toxic. *Id.* at 623–24.

While the later findings regarding 2'-CDG's toxicity certainly make claims regarding the reasonableness of any expectation of success less credible, on this record, the panel did not act beyond the pale in concluding that the district court's factual conclusion regarding the existence

of a reasonable expectation of success was not clearly erroneous.[4] The panel's decision to affirm the district court's findings does not foreclose the possibility that post-invention evidence regarding the properties of either the invention or the prior art might be persuasive in the appropriate case. BMS simply did not make a record which would support the conclusion that they were in this case.

BMS and the amici next contend that the panel inappropriately discounted the significance of unexpected results when the panel parsed unexpected results into "differences in kind" and "differences in degree." They argue that the panel's treatment of entecavir's unexpected properties as mere differences in degree from 2'-CDG's properties diminishes the potentially meaningful distinctions between two compounds by reducing the nuanced unexpected results inquiry to a question of degree versus kind. According to BMS and the amici, this characterization of what may be considered unexpected results creates impossible hurdles for the pharmaceutical industry to overcome, where slight differences between compounds can translate into life or death for a patient.

In its discussion of unexpected results, the panel explained that "[w]hen assessing unexpected properties . . . we must evaluate the significance and 'kind' of expected results along with the unexpected results." *Bristol-Myers Squibb Co.*, 752 F.3d at 977. This statement is consistent with our precedent that one should consider the substan-

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[4] While I agree with all of the concerns thoughtfully expressed by Judge Taranto, as he acknowledges, the current record does not permit us to reach those concerns. BMS did not argue that there was insufficient evidence to indicate that a modification of 2'-CDG would be therapeutically effective, and there is no evidence in the record that skilled artisans at the time doubted that it would be.

tiality of the differences between the properties of the prior art and those of the invention to determine the significance of those differences. *See In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) ("Mere improvement in properties does not always suffice to show unexpected results. . . . [W]hen an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of evidence* to the contrary."); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) ("[T]he mere submission of some evidence that a new compound possesses some unpredictable properties does not require an automatic conclusion of nonobviousness in every case."); *In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) ("In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination."); *In re Corkill*, 771 F.2d 1496, 1501 (Fed. Cir. 1985) ("A greater than expected result is an evidentiary factor pertinent to the legal conclusion of [] obviousness.").

While reading the panel's statement that a "'mere difference in degree' is insufficient" to render a compound patentable out of context admittedly could lead to some confusion, the panel's entire discussion of unexpected results makes clear that one must consider the extent of the differences between properties of the prior art and the invention to determine the weight such evidence should be given in the obviousness analysis. The reference to differences in kind versus differences in degree was merely illustrative of how one can assess unexpected properties—it was not essential to the panel's finding that it would defer to the district court's factual finding that the results upon which BMS relied were not truly unexpected or substantial. *Bristol-Myers Squibb Co.*, 752 F.3d at 978. Accordingly, I do not believe the panel's mere use of the phrasing to which BMS objects inappropriately

reduces the question of unexpected results to a purely mechanical application of degree versus kind.

BMS and the amici next contend that the panel endorsed the use of a burden-shifting framework, wherein the burden shifted to the patentee once the alleged infringer established a *prima facie* case of obviousness. The panel neither used nor endorsed a burden-shifting analysis, however; it said explicitly that it was employing a holistic approach to obviousness. *Id.* at 976–77 (considering Teva's strong evidence of obviousness alongside BMS's arguments relating to secondary considerations of nonobviousness); *id.* at 977 (explaining that "[s]econdary considerations of nonobviousness 'must always when present be considered'" (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075–76, 1079 (Fed. Cir. 2012))).[5] Again, the amici and BMS see ghosts that are simply not there.

Lastly, BMS and the amici argue that the panel decision supports comparing the objective indicia of nonobviousness against one another, allowing some to offset others. As the panel itself stated, "[it] under[stood] the district court to be noting that some categories of [objective indicia] evidence simply were not as helpful to BMS's case as others. [The panel did] not read the opinion as suggesting that unhelpful evidence somehow diminished

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[5] Indeed, the district court made clear that it too understood the importance of objective considerations in the obviousness inquiry. *Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 675 (noting that objective evidence of nonobviousness must be "considered collectively" with evidence of obviousness, may not be "after-the-fact considerations" and may not be "relegated to 'secondary status'") (citing *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1078). It just disagreed with the weight BMS asked that they be given in this case.

the strength of the more persuasive forms of evidence." *Id.* at 979. Here, BMS and the amici simply mischaracterize the panel opinion.

Ultimately, a case is won or lost on the record. At the district court, BMS's own expert, Dr. Schneller, conceded that 2'-CDG would have been considered as a lead compound by one skilled in the art and acknowledged that 2'-CDG was *actually* being used as a lead compound at the time of entecavir's invention. *Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 663 ("BMS's expert, Dr. Schneller, . . . repeatedly testified at trial that [SRI and Glaxo] chemists *were, in fact*, treating and using 2'-CDG as a lead compound" during the time of the invention.); *id.* at 664 ("[T]he testimony of [BMS's] own expert at trial repeatedly and conclusively established that researchers were, in fact, treating and using 2'-CDG as a lead compound in the relevant time period."). Additionally, Dr. Schneller admitted that a skilled artisan could have been led to modify 2'-CDG in such a way to arrive at the claimed invention. *Id.* at 665 ("Dr. Schneller . . . agreed that when a lead compound is selected, a chemist would seek to make conservative changes to that structure."); *id.* at 670–71 (Dr. Schneller stated in his expert report and on cross examination that in light of the prior art a skilled artisan could have been led to substitute an exocyclic methylene group at the 5 prime position of 2'-CDG). In light of these admissions, the district court concluded that, in "almost every significant portion of [its] case, Teva's position was not only bolstered by the opinion of its expert, Dr. Heathcock, but also by the testimony of BMS's expert, Dr. Schneller." *Id*. at 686.

Despite the testimony of its own expert below, on appeal, BMS originally focused on the district court's alleged error in concluding that a skilled artisan would have selected 2'-CDG as a lead compound and modified it to arrive at the claimed invention. Reference to evidence of entecavir's unexpected properties was raised almost as an

afterthought in BMS's opening brief, as was its focus on the reasonable expectation of success prong of the motivation to combine inquiry before the district court. Now, BMS and the amici adopt a "sky is falling" approach to what is simply a fact dependent opinion. The opinion makes no dramatic changes to the law, closes no doors on what evidence may be considered in undertaking an obviousness inquiry, establishes no hard and fast tests for what results might be considered unexpected in a case involving a pharmaceutical compound, and does not improperly shift the burden of proof or denigrate the importance of objective indicia of non-obviousness.[6] On this record and upon a fair reading of the panel opinion, I do not believe en banc consideration is warranted.

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[6] I do not discount the fact that, in dissent from this denial of en banc, Judges Newman, Lourie, and Reyna are concerned that the panel opinion did go too far and that Judge Taranto at least believes the opinion can be read—fairly or not—as having done so. We all agree on the law, we simply disagree whether this opinion is sufficiently at odds with it to warrant en banc consideration.

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Appeal from the United States District Court for the District of Delaware in No. 10-CV-0805, Magistrate Judge Christopher J. Burke.

NEWMAN, *Circuit Judge*, with whom LOURIE and REYNA, *Circuit Judges*, join, dissenting from the denial of the petition for rehearing en banc.

This appeal concerns a patent owned by Bristol-Myers Squibb Company on the product entecavir, a medicinal product for treatment of hepatitis B. Litigation arose under the provisions of the Hatch-Waxman Act, upon the filing by Teva Pharmaceuticals USA of an Abbreviated New Drug Application Paragraph IV Certification. A

panel of this court held the patent invalid,[1] creating several new standards for determination of obviousness. For example, the court deemed it irrelevant to the obviousness determination that the prior art "lead compound," the carbocyclic analog of 2′-deoxyguanosine (2′-CDG), is highly toxic to humans, whereas the new product entecavir is non-toxic. Bristol-Myers requests rehearing en banc, arguing that the court has misapplied statute and precedent.

This case has aroused extensive commentary, particularly in the chemical and pharmaceutical fields; the request for rehearing en banc is supported by much of the nation's research-based industry, which has filed briefs as amici curiae to point out the disincentives and uncertainties flowing from the court's rulings. As summarized by amicus Intellectual Property Owners Association:

> This decision introduces substantial uncertainty into what appeared to be a clear legal standard; allowing this uncertainty to fester would affect countless pending and future cases. Obviousness is an issue in most patent examinations, litigations, and administrative proceedings. Particularly in unpredictable chemical and pharmaceutical fields, unexpected results evidencing differences and objective considerations can tip the balance between obviousness and non-obviousness. Patent owners would benefit from the certainty of an en banc ruling on when and how later-discovered differences between an invention and prior art may be considered in the obviousness analysis.

Brief of Amicus Curiae Intellectual Property Owners Association in Support of Rehearing En Banc at 6-7.

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[1] *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014).

I outline the several conflicts with precedent here produced; for until this case, inventors could confidently establish patentability of a new product or a new use by showing that the new property or use was unexpected in light of the prior art.

1. Restriction on comparative data showing unexpected properties

The court held that entecavir's unexpected properties did not render it nonobvious in patent terms because "additional unexpected properties, however, did not upset an already established motivation to modify a prior art compound based on the expected properties of the resulting compound." *Bristol-Myers*, 752 F.3d at 976. The court's hindsight decision that Bristol-Myers merely "ma[de] the minor modification to arrive at entecavir," *id.* at 973, while ignoring the unexpected differences in properties between entecavir and the prior art compound, conflicts with the entirety of precedent on the law of obviousness.

When a new product (or device or method) is discovered, its nonobviousness in patent terms often is demonstrated by evidence of whether the new product (or device or method) possesses properties not possessed by similar products. The mechanism for providing this evidence is the submission of comparative data in affidavits or declarations filed pursuant to USPTO Rule 132, 37 C.F.R. §1.132. Such data may involve new experiments performed on the invention and the prior art for purposes of comparison, and information already known although not in comparative form. *See, e.g.*, *In re Chupp*, 816 F.2d 643, 644 (Fed. Cir. 1987) ("To rebut the *prima facie* case of obviousness, Chupp submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides. . . . It is undisputed that the claimed compound gave superior

results . . . ."); *In re Payne*, 606 F.2d 303, 306, 316 (CCPA 1979) (in response to an obviousness rejection based on prior art, the inventor provided data that "purportedly establishes an unexpectedly superior scope and level of pesticidal activity of the claimed compounds in a comparison of the most representative compound of" the prior art).

Such comparative data need not have been previously available or known to the art at the time of the invention. In *In re Miller*, 197 F.2d 340, 342 (CCPA 1952), the court called for the "making of comparative tests" if needed to support unexpected results. This is established practice. *See, e.g.*, *In re Orfeo*, 440 F.2d 439, 441 (CCPA 1971) (applicants "have the right to have considered the Rule 132 affidavit which allegedly shows new and unexpected results"); *In re Khelghatian*, 364 F.2d 870, 872 (CCPA 1966):

> There appears to be agreement of the parties that essential to the proper resolution of this issue is a consideration of all the record evidence, including an affidavit filed under Rule 132. Such has been the law in this court for several years, and that regardless of whether any "doubt" as to patentability exists upon an examination of the prior art alone.

Precedent is clear that the information and comparative data presented as evidence of nonobviousness need not have existed before the patent application was filed. *See, e.g.*, *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011):

> [I]t would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application.

See also Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004):

> There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.

Information learned after the patent application was filed may provide evidence of unexpected or unpredicted properties. *E.g.*, *In re Zenitz*, 333 F.2d 924, 925, 927 (CCPA 1964) (later discovered hypotensive and tranquilizing properties that were not described in the specification could render the claimed compounds nonobvious and thus patentable); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014):

> Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis, here referring to the improved kidney and blood vessel function that were observed after the patent application was filed. That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest.

Comparisons of newly found properties of both the invention and the prior art are routinely presented as evidence in determinations of obviousness. In *Leo Pharmaceutical Products, LTD. v. Kappos*, 726 F.3d 1346 (Fed. Cir. 2013), the patentee during reexamination conducted tests of the prior art and showed that the reference formulations resulted in significant degradation of the vitamin D analog and corticosteroid. In considering this post-

invention testing of the prior art, this court stated "[t]hese test results are a strong indication that the '013 patent's combination of known elements yields more than just predictable results," and reversed the Board's obviousness determination. *Id.* at 1358.

The provision of comparative data, whether or not the data were available before the patent application was filed, is long-established practice. *See In re Payne*, 606 F.2d at 315-16 ("A prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. Direct or indirect comparative testing between the claimed compounds and the closest prior art may be necessary." (citing *In re Papesch*, 315 F.2d 381, 386-87 (CCPA 1963))); *In re Merchant*, 575 F.2d 865, 869 (CCPA 1978) ("An applicant relying upon a comparative showing to rebut a prima facie case must compare his claimed invention with the closest prior art."); *In re Miller*, 197 F.2d 340, 342 (CCPA 1952) ("Where, as here, results superior to those produced by the references of the prior art, or public knowledge and use, constitute the basis for the claim of invention, the making of comparative tests and the establishment of the unexpected and superior results never before attained must be established by a proper showing.").

Despite this overwhelming precedent, the court declined to weigh that the designated lead compound 2′-CDG is highly toxic and concededly is useless in treating hepatitis B. Such information cannot be ignored, although it was not observed until the prior art compound was tested in mammals, after the entecavir patent application was filed. This does not render this unexpected difference irrelevant to patentability, as a matter of law or logic. In *In re Papesch* the court explained:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are

> one and the same thing. . . . [T]he thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison.

315 F.2d at 391.

Our colleagues in concurrence disregard the entirety of precedent and practice. The amici curiae protest the court's changes of law and understanding as confusing, unnecessary, and contrary to the public interest in development of useful and beneficial new products. Amicus curiae the Biotechnology Industry Organization reminds the court of the new statutory pressures for early filing, now that the patent goes to the first inventor to file, not the first to invent:

> The AIA's new first-to-file system puts pressure on companies to file early, lest they lose priority. But, under the panel's approach, innovators might be better off waiting, in case new, unexpected differences between the invention and prior art come to light during clinical testing. There is no reason to put innovators to that difficult choice.

Brief of Amicus Curiae Biotechnology Industry Organization in Support of Rehearing En Banc at 7.

If there is now to be a major restriction on the evidence that can be adduced in support of patentability of new and improved products, such change of law should be determined en banc.

2. The misapplication of "secondary considerations"

Information about the "secondary considerations" of nonobviousness, *see Graham v. John Deere Co.*, 383 U.S. 1

(1966), is often based on post-filing knowledge and data. Such information includes "commercial success, long felt but unsolved needs, failure of others, etc.," *id.* at 17, and tends to become manifest after the patent application is filed and the invention is used. "Evidence of secondary considerations may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

Emphasizing the characteristics of medicinal and biological products, amicus curiae Pharmaceutical Research and Manufacturers of America observes that the objective indicia of nonobviousness do not come into existence until after the patent application was filed. If there is now to be some restriction on reliance on such information, it should be clearly stated and contrary precedent should be overruled.

3. The holding that an unexpected property is insufficient "by itself" to show nonobviousness

The court stated that "unexpected results do not *per se* defeat, or prevent, the finding that a modification to a lead compound will yield expected, beneficial properties." *Bristol-Myers*, 752 F.3d at 976. The court further stated that "an unexpected result or property does not by itself support a finding of nonobviousness." *Id.* To the contrary, an unexpected result or property is the touchstone of nonobviousness.

Although the court recognized that entecavir has the "unexpected properties [of]: (1) high potency against hepatitis B, (2) a larger than expected therapeutic window, and (3) a high genetic barrier to resistance," *id.* at 977, the court held that these unexpected properties were expected because the prior art had these properties to some failed extent. The court postulated that entecavir's non-toxicity was "not unexpected in light of the structurally similar 2′-CDG," *id.* at 978, although the toxicity of 2′-

CDG was so high that it was abandoned as a potential treatment for hepatitis B.

Precedent directly contradicts the court's position. An unexpected property "by itself" can, indeed, support a finding of nonobviousness. This court stated in *In re Soni*:

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. . . . [W]hen an applicant demonstrates substantially improved results, as Soni did here, and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.

54 F.3d 746, 750-51 (Fed. Cir. 1995).

This principle is—or was—beyond dispute, as illustrated on a vast variety of facts. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) ("If a patent challenger makes a prima facie showing of obviousness, the owner may rebut based on 'unexpected results' by demonstrating 'that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.' (quoting *In re Soni*, 54 F.3d at 750)); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 969-70 (Fed. Cir. 2006) (affirming nonobviousness over prima facie case based solely on evidence of unexpected results); *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (observing that "a prima facie case of obviousness can be rebutted if the applicant (1)

can establish 'the existence of unexpected properties in the range claimed' or (2) can show 'that the art in any material respect taught away' from the claimed invention." (quoting *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974))); *In re Corkill*, 771 F.2d 1496, 1501 (Fed. Cir. 1985) ("A greater than expected result is an evidentiary factor pertinent to the legal conclusion of the obviousness *vel non* of the claims at issue." (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966))); *In re De Blauwe*, 736 F.2d 699, 706 n.8 (Fed. Cir. 1984) ("A proper showing of unexpected results will rebut a prima facie case of obviousness." (citing *In re Fenn*, 639 F.2d 762 (CCPA 1981); *In re Murch*, 464 F.2d 1051 (CCPA 1972))); *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972) ("The fact that an invention provides results which would not have been expected by those skilled in the art is strong evidence in rebuttal of an assertion that the invention would have been obvious.").

The court's apparent departure from this principle, and its holding that not all properties need be considered in determining obviousness, is a primary focus of the concerns stated by the amici curiae. Amicus curiae Bay Area Bioscience Association writes that:

> For many newly discovered pharmaceuticals, their truly innovative and life-saving properties are often not discovered until well-controlled clinical trials or even post-marketing studies have been conducted—events that occur well after the filing date of the patent-in-suit. Indeed, this is particularly so in the area of personalized medicine, where novel therapeutic treatments are tailored to a particular patient's genetic makeup.

Brief of Amicus Curiae Bay Area Bioscience Association in Support of Rehearing En Banc at 7. Again, if the law is to be changed and precedent discarded, en banc attention

is required, rather than discordant conflict with precedent.

4. The court's oversimplified distinction between "difference in degree" and "difference in kind"

The court held that a "mere difference in degree" is "insufficient" to render a compound patentable. 752 F.3d at 977. The flaw in this generalization is apparent from its application here, where the court held that a new and effective non-toxic treatment for hepatitis B is merely a difference in degree from a highly toxic and useless treatment for hepatitis B.

Precedent has placed the usage "difference in degree" in a more useful context:

> Whether the difference between the claimed invention and the prior art is a difference "in kind" or a difference "in degree" is not mentioned in section 103. Section 103 simply requires a determination as to whether the invention as a whole would have been obvious to one of ordinary skill in the art at the time of appellant's invention. An unexpected increase in physiological activity may be persuasive evidence of unobviousness.

In re Wagner, 371 F.2d 877, 885 (CCPA 1967) (citing *In re Grier*, 342 F.2d 120 (CCPA 1965)); *see also In re Chupp*, 816 F.2d at 644, 646-47 ("selectivity factors (crop safety combined with weed-killing activity) at least five times greater than those of closest prior art compounds" were sufficient evidence of unexpected difference in properties to rebut prima facie case of obviousness); *In re Wiechert*, 370 F.2d 927, 932 (CCPA 1967) ("Appellant contends that obviousness of a novel compound is to be decided not only from a comparison of its structural formula with that of the prior art compound, but from all properties of the compounds. . . . We think appellant's contentions have merit . . . . As we indicated in *In re Lohr*, 317 F.2d 388

(CCPA 1963), it is possible to obtain a patent where the showing proves substantially greater effectiveness. . . . In the case at bar, we are impressed by the 7-fold improvement in activity and, in the absence of valid countervailing evidence, we find the claimed compounds to be unobvious.").

The stage at which an obvious difference in degree becomes an unobvious difference in kind is based on the particular subject matter. On the undisputed facts herein, the prior art compound 2′-CDG was found to be toxic to mammals, whereas entecavir is non-toxic to mammals. This cannot be reasonably viewed as a "mere difference in degree."

All of the amici curiae expressed concern about the negative impact on development of new and improved products flowing from the court's fresh uncertainty on the availability of reliable patent rights. No policy reason has been offered by the court, for its further restrictions on access to patenting. From my colleagues' refusal to review this ruling en banc, I respectfully dissent.

United States Court of Appeals for the Federal Circuit

BRISTOL-MYERS SQUIBB COMPANY,
Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Appellee.

2013-1306

Appeal from the United States District Court for the District of Delaware in No. 10-CV-0805, Magistrate Judge Christopher J. Burke.

TARANTO, *Circuit Judge*, with whom LOURIE and REYNA, *Circuit Judges*, join, dissenting from the denial of the petition for rehearing en banc.

Bristol-Myers created a new chemical compound: entecavir. Its structure is a modification of a prior-art compound, apparently a common phenomenon in pharmaceutical chemistry, where small changes can make large differences. The prior-art compound (2′-CDG) was described in published papers. It had shown excellent activity against certain viruses, including the hepatitis B virus, in tests on cell lines in in vitro experiments; but it had never been tested even in animals, let alone humans, whether for efficacy or toxicity. Bristol-Myers's novel compound proved to be effective and nontoxic (safe) for

the treatment of hepatitis B, and it was patented and came to be approved and widely used for that purpose. In contrast, the prior-art compound never came to have any human-therapeutic use, because, just after Bristol-Myers sought its patent, 2′-CDG was tested in animals for the first time, and the tests so conclusively showed it to be toxic that it has never been used in humans. In short, the Bristol-Myers compound, which is a novel molecule, is dramatically different from the prior-art compound in providing practical human benefits: one provides such benefits, the other does not. But that difference was identified only after Bristol-Myers filed for its patent, because the prior-art compound, not having been tested in animals or humans, was not then known to be toxic.

After a trial, the district court invalidated the asserted claim of the Bristol-Myers patent under 35 U.S.C. § 103(a) (2006), holding that the new compound would have been obvious to a person of ordinary skill in the pertinent art at the time of the invention (here, the filing date of the patent application). In so holding, the court determined that such a hypothetical skilled artisan would have had a reasonable expectation of success in achieving therapeutic usefulness in humans and would not have found the favorable safety/efficacy profile of entecavir to be unexpected, because, at that time, the prior-art compound, never having been tested even in animals, was not known to be toxic. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 630–33 (D. Del. 2013). On appeal, the panel in this case affirmed those determinations and the ultimate holding of obviousness. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014).

In considering whether en banc review is warranted, I focus on the doctrinal significance of the panel decision from two perspectives—looking at what the decision *says*, and at what it seems to *decide* on the facts. As to the first: It is a well-recognized principle, and one essential to

our system of precedent, that statements in opinions must be read in context, considering their role in the decision and the facts of the case.[1] Nevertheless, advocates often ignore that principle, relying on phrases and sentences found through database word searches without reading the whole opinion, and arguing for a precedential effect that is unwarranted. I here point out why the panel opinion should not be taken to stand for certain propositions for which advocates are likely to cite it.

As to the second: Although it is not certain, the panel, in what it actually decided in affirming invalidity for obviousness on the recited facts, may have dismissed post-filing discoveries of prior-art compounds' true properties

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[1] *See*, *e.g.*, *R.A.V. v. City of St. Paul*, 505 U.S. 377, 386–87 n.5 (1992); *Armour & Co. v. Wantock*, 323 U.S. 126, 132–33 (1944); *Sterling v. Constantin*, 287 U.S. 378, 400 (1932); *Nat'l Am. Ins. Co. v. United States*, 498 F.3d 1301, 1306 (Fed. Cir. 2007); *Perez v. Dep't of Justice*, 480 F.3d 1309, 1312 (Fed. Cir. 2007); *N. States Power Co. v. United States*, 224 F.3d 1361, 1367 (Fed. Cir. 2000); *Fromson v. W. Litho Plate & Supply Co.*, 853 F.2d 1568, 1578 (Fed. Cir. 1988) ("Cases should not be cited for mere words. What counts is what the court did in a cited case."), overruled on other grounds by *Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed. Cir. 2004); *In re Hounsfield*, 699 F.2d 1320, 1323 (Fed. Cir. 1983) ("Although some of the foregoing judicial statements standing alone could be read to support the principle the Board here applied, those statements must be read in the light of the facts of the cases, the precise issues to be resolved therein, and the courts' holdings."); *In re Van Ornum*, 686 F.2d 937, 946 (CCPA 1982) ("Precedents are of value for what they *decide,* not for every sentence they contain."); *In re Ruscetta*, 255 F.2d 687, 689 (CCPA 1958).

as categorically irrelevant to the statutory inquiry. Or it may have more narrowly deemed insufficient the evidence here—that, the first time the prior-art compound was tested in animals, it proved so toxic that it had to be abandoned as a candidate for human-therapeutic use. Even if the panel merely rejected the particular post-filing evidence here as insufficient, it is significant (for how the decision will be invoked as precedent) that the panel did not give any case-specific reasons for doing so except timing: the discovery of the prior-art compound's toxicity post-dated the invention. The panel decision seems highly likely to be viewed as addressing the timing-of-evidence question—whether generally or in this context. And that question is worthy of further attention.

Although I am not confident of the answers, I think that the ruling raises questions about core aspects of the widely used approach to obviousness analysis—particularly, the proper meaning of the related elements, "reasonable expectation of success" and "unexpected results." Those questions would benefit from plenary consideration. In panel review, case-specific applications on complex facts necessarily consume almost all of the space of parties' briefs, and attention is focused almost exclusively on this court's own precedents. En banc review would allow a focus on and full analysis of the doctrinal issues, considering the language of section 103 (what it resolves and what it leaves open); the role of section 103 in the statute as a whole (which places a premium on early filing); Supreme Court precedents elaborating on the policy of section 103; our own precedents; congressional actions in light of those precedents; and pertinent, reliable information that may bear on assessing the real-world consequences of one answer or another in an industry where research is especially expensive and uncertain. The widened inquiry seems to me worthwhile.

A

1. The panel stated that this court's en banc decision in *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990), "explain[ed] that an unexpected result or property does not by itself support a finding of nonobviousness." *Bristol-Myers*, 752 F.3d at 976 (citing *Dillon*, 919 F.2d at 693, 697). That statement must not be read out of context to declare that evidence of unexpected results cannot by itself support an ultimate finding that a challenger has failed to demonstrate obviousness by clear and convincing evidence.

First: The panel made the statement only in discussing whether to uphold the determination about a key component of the traditional *prima facie* case in an obviousness challenge—that the hypothetical skilled artisan would have had not only a reason to create the new chemical compound (the claimed invention here) but also "a reasonable expectation of success" concerning its favorable human-therapeutic profile. *Bristol-Myers*, 752 F.3d at 976–77. The panel was not discussing whether, even if there were a sustainable finding of a reasonable expectation of that success, evidence of particular unexpected results—*e.g.*, unexpectedly great efficacy or safety in the expected use, or efficacy and safety for an additional, unexpected use—could nevertheless support an ultimate finding of non-obviousness. Indeed, reading the statement to draw that conclusion would render immaterial the extensive discussion of unexpected results that comes next in the opinion. The panel did not introduce that discussion by suggesting that it was an "even if" analysis unnecessary to the bottom-line conclusion.

Second: *Dillon* itself does not establish that evidence of unexpected results cannot support rejection of an obviousness challenge despite supported findings of the elements of a *prima facie* case. The issue addressed and decided in *Dillon* was only what was needed to establish the *prima facie* case in the first place; and *Dillon* took

care to stress that it was only that issue it was deciding, not the ultimate determination of obviousness. 919 F.2d at 697 (distinguishing *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963), on ground that *Papesch* "did not deal with the requirements for establishing a *prima facie* case," stating: "*Papesch* is irrelevant to the question of the requirements for a *prima facie* case, which is the question we have here"). *Dillon* did not need to consider whether unexpected results could support rejection of a section 103 challenge despite a supported finding of the *prima facie* case elements, because *Dillon* concluded that the PTO properly found no unexpected results: "[Applicant] did not present any showing of data to the effect that her compositions had properties not possessed by the prior art compositions or that they possessed them to an unexpectedly greater degree." 919 F.2d at 693.

Third: The panel in this case, like the court in *Dillon*, had no occasion to rule on the doctrinal relationship between a finding of unexpected results and a finding of the *prima facie* case elements. The panel upheld the district court's determination that there were *no* appreciable unexpected results. *Bristol-Myers*, 752 F.3d at 977–78; *see id.* at 978 ("[T]he district court's findings reflect that one of skill in the art would have expected entecavir's hepatitis B's efficacy, safety, and therapeutic window based on one's knowledge of 2′-CDG."); *Bristol-Myers*, 923 F. Supp. 2d at 686 ("No witness testified that the [low toxicity] of the drug would have been 'unexpected.'"). On that premise, there were no unexpected results whose relationship to the *prima facie* case the panel had to consider.[2]

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[2] The panel likewise had no occasion to address broader issues concerning the familiar use of a "*prima facie* case" as a sequence-of-presentation, issue-organizing tool in a challenge to an issued patent, for which invalidi-

2. The panel decision also does not establish a precedent for the proposition that, putting aside the post-filing evidence, the proof of "reasonable expectation of success"—based entirely on in vitro experiments with the lead compound—was adequate. Bristol-Myers never argued otherwise to the court; it argued only that, once the post-filing evidence of 2′-CDG is considered, the proof of reasonable expectation of success was inadequate and the proof of unexpected results in any event compelling. Inadequacy apart from the post-filing evidence not having been argued, the panel opinion is not precedent for deeming the pre-filing evidence inadequate.[3]

This is worth noting because it seems to me a serious question whether, in this case and perhaps more generally, the purely in vitro experiments on the lead compound should be deemed to establish a "reasonable" expectation of success. The success that must be reasonably expected in this case would, I think, have to be success in what motivated the investment in the research—an acceptable safety/efficacy profile for human-therapeutic use.[4] Thus,

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ty requires clear and convincing proof, *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2252 (2011). *Cf. U.S. Postal Serv. Bd. of Governors v. Aikens*, 460 U.S. 711, 714–16 (1983) (discussing burden of persuasion and presentation-of-proof scheme in discrimination cases); *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 147–49 (2000) (same).

[3] *See, e.g.*, *District of Columbia v. Heller*, 554 U.S. 570, 625 n.25 (2008); *United States v. Verdugo-Urquidez*, 494 U.S. 259, 272 (1990); *United States v. L.A. Tucker Truck Lines, Inc.*, 344 U.S. 33, 38 (1952); *JVC Co. of Am. v. United States*, 234 F.3d 1348, 1353–54 (Fed. Cir. 2000) (citing earlier cases).

[4] *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013); *In re Cyclobenzaprine Hydrochlo-*

whatever the precise meaning of "reasonable expectation"—a matter worth clarifying, as discussed *infra*—Teva had to show that a hypothetical skilled artisan would have had a *reasonable* expectation of acceptable safety of entecavir in humans in October 1990, when Bristol-Myers filed for its patent. And such an expectation, it appears undisputed, depended entirely on showing such an artisan's reasonable expectation, at the time, that the lead compound, 2′-CDG, would be acceptably safe in humans.

There is a serious question whether any such expectation was reasonable, given that 2′-CDG had been tested only in in vitro experiments—never even in animals, let alone humans. As a general matter, it may be that in vitro tests are not reliably predictive of human safety.[5]

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ride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1070 (Fed. Cir. 2012); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000).

[5] *See* Fed. Judicial Ctr., *Reference Manual on Scientific Evidence* 645 (3d ed. 2011) ("Relatively few [in vitro toxicity tests] have been validated by replication in many different laboratories or by comparison with outcomes in animal studies to determine if they are predictive of whole animal or human toxicity."); *In re Gangadharam*, 1989 WL 127023, at *2 (Fed. Cir. Oct. 27, 1989) (noting that a prior art's "remarking that the positive in vitro results 'favored' use in vivo does not meet the statutory standard" of obviousness); *see also* Anna Astashkina et al., *A Critical Evaluation of In Vitro Cell Culture Models for High-Throughput Drug Screening and Toxicity*, 134 Pharmacology & Therapeutics 82, 82, 94 (2012) (noting "strong evidence that in vitro cell-based assays and [even] subsequent preclinical in vivo studies do not yet provide sufficient pharmacological and toxicity data or reliable

Although statistics require careful examination to be used responsibly, I note that amici have pointed us to literature indicating that only small percentages of compounds that start in the laboratory make it out the other end of the drug-development process.[6]

It may well be, of course, that in vitro testing supports a sound expectation about probable human safety for certain compounds even if it does not do so generally. But that is a matter to be addressed by scientific evidence about the particular compounds at issue in a given case. Here, with Bristol-Myers not having contested the point, the panel had no occasion to scrutinize the record to determine if there was evidence of a reliable basis for any prediction of *human* safety for 2′-CDG in October 1990. Optimism about the compound is not the same as a reasonably grounded prediction. And testimony that 2′-CDG had a "very good therapeutic window" *in an in vitro test*—which is all that the quote refers to, because 2′-CDG had never been given as "therapy" or even put into animals or humans—does not support safety in humans without sound evidence allowing the inference, none of which is apparent. *Bristol-Myers*, 752 F.3d at 971, 974, 978. The issue not having been contested, the panel decision cannot be taken to have resolved the issue.

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predictive capacity for understanding drug candidate performance in vivo").

[6] *See*, *e.g.*, Henry Grabowski, *Patents, Innovation, and Access to New Pharmaceuticals*, 5 J. Int'l Econ. L. 849, 849–51 (2002) ("[F]ewer than 1% of the compounds examined in the pre-clinical period make it into human testing."); Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, Nature Biotechnology Jan. 2014, at 41–42, 47 (10-15% of drugs entering human testing emerge as marketed drugs).

B

As already noted, the panel opinion may be read by future litigants to suggest that any evaluation of prior art must focus exclusively on what was known about the prior art's properties, and on that basis expected about entecavir, at the time of the Bristol-Myers invention. *See Bristol-Myers*, 752 F.3d at 974, 977, 978. The panel opinion ultimately approves the district court's decision to excise from its analysis any consideration of 2′-CDG's later-discovered, severe toxicity. *Id.* at 978 ("The district court ultimately made the correct direct comparison of the patented compound to 2′–CDG, noting that prior art compounds, 'including 2′–CDG,' 'showed effectiveness against hepatitis B *without known toxicity issues*.'") (emphasis added) (quoting *Bristol-Myers*, 923 F. Supp. 2d at 685). The timing-of-evidence reasoning seems at the heart of the obviousness invalidation. It raises questions that I think warrant further exploration.

1. Judge Newman identifies ways in which the panel's approach to the timing-of-evidence question seems in tension with this court's precedents. It appears that, at least since our predecessor court's decision in *In re Papesch*, 315 F.2d 381 (CCPA 1963), the analysis of obviousness of new chemical inventions has involved "liberal consideration of post-invention evidence." Rebecca S. Eisenberg, *Pharma's Nonobvious Problem*, 12 Lewis & Clark L. Rev. 375, 395 (2008). The reason seems clear: "often it takes time to determine the properties of a new chemical through testing and observation that cannot take place until after the chemical is in hand," *id.* at 396, and the statute has always provided an incentive to file early once the chemical is in hand (lest priority be lost), an incentive now enhanced by the 2011 adoption of a first-inventor-to-file system. Moreover, Judge Newman notes that the post-filing experiments comparing properties of the invention and prior-art compounds would seem often to have developed new information about both the inven-

tion and the prior-art compound. These precedents and past practices raise questions about the panel's ruling.[7]

2. The statutory language does not itself provide an answer to the question of post-filing evidence.[8] It is true

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[7] In still other ways, obviousness analysis routinely considers relevant facts not in existence at the time of patent filing, *e.g.*, commercial success and proven meeting of a long-felt need. *See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332–33 (Fed. Cir. 2009).

[8] Section 103, reflecting the first-inventor-to-file system adopted in 2011, now reads: "A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103.

35 U.S.C. § 103(a) (2006) was similar but reflected the pre-2011 first-to-invent system: "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

that the language directs courts (and the PTO) to ask a question about the time "before the effective filing date of the claimed invention" (the "time the invention was made" in the pre-2011 version). But the question is not what certain people in the field in fact thought at that time. Rather—to note three aspects of the language (others may be relevant too)—the question is whether (a) the claimed invention "as a whole" (b) "would have been" obvious to a (c) "person having ordinary skill in the art."

As to the first of those elements, the *Papesch* doctrine has long treated all properties, including later discovered ones, as part of the invention "as a whole." As to the third, the "person having ordinary skill in the art" is not a real-world person, but a hypothetical person, constructed in applying the provision to create a standard of patentability that effectuates the provision's policy.[9] As to the second, the statute uses the verb phrase "would have been." Grammatically, that formulation invokes a hypothetical situation dependent on some "if" condition (would have been obvious if "x" had been true). In section 103, however, the required condition is not stated; there is no "if" clause.

As a result, the statutory language itself requires courts to fill in the conditions for the hypothetical inquiry by an analysis of the provision's history, role in the statute, and purpose, always considering workability of any approach. It is common to hypothesize knowledge of all pertinent prior art. *See In re Moreton*, 288 F.2d 940, 941 (CCPA 1961); *In re Citron*, 251 F.2d 619, 620 (CCPA 1958). It has been suggested, too, that the hypothetical inquiries should not take as a given the current amassing

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[9] *E.g.*, *Bristol-Myers*, 752 F.3d at 978; *Norgren, Inc. v. Int'l Trade Comm'n*, 699 F.3d 1317, 1327 (Fed. Cir. 2012); *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1454 (Fed. Cir. 1984).

and organizing of resources and talent into firms that undertake risky, expensive research, which might not exist without patent protection. *See* Michael Abramowicz & John F. Duffy, *The Inducement Standard of Patentability*, 120 Yale L.J. 1590, 1614–16 (2011). Whatever the proper approach, however, it is one that must be developed by looking at more than the effective-date-of-filing (previously, invention-date) phrase in section 103, whose terms as a whole call for a hypothetical inquiry requiring judicial definition.

3. The proper analysis of the post-filing evidence regarding 2′-CDG would seem to focus on two closely related phrases that identify standard parts of our obviousness analysis: "reasonable expectation of success" and "unexpected results." Both phrases evidently bear several different potential meanings and so would benefit from clarification. And the identification of the proper meanings seems to have a strong bearing on whether the post-filing evidence here is material.

The phrase "reasonable expectation of success" on its face requires that any expectation of success be "reasonable." The same reasonableness requirement would seem implicit, too, in the hypothetical character of the skilled artisan whose expectations count. The hypothetical character of the person doing any expecting seemingly also should mean that "unexpected results" contains a reasonableness requirement. What must be "reasonable" are (hypothetical) "expectations." But "expectation" is a term that covers different ground in different circumstances.

Clarifying these concepts seems important here. Should a reasonable expectation mean a mere educated guess or surmise or plausible possibility? Should it mean an affirmative well-grounded prediction, using a 50% or other probability, based on the standards that scientists would use professionally to assert such predictions—

whether in a scientific journal or in making a decision about how to allocate scarce research funding? Depending on the meaning of "expectation," should the reasonableness of the expectation consider not just what evidence has been developed but also what evidence could easily be developed but has not yet been—so that, for example, it may be irresponsible to assert an expectation in the absence of such available but not-yet-secured evidence?

We have tied the "reasonable expectation of success" standard to the Supreme Court's use of "predictable" in *KSR*, 550 U.S. at 416, 417, 421. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). That precedent suggests a higher rather than lower standard for "reasonable expectation."

Perhaps the statutory policy of section 103 does as well. The Supreme Court has suggested the policy (not for case-by-case application but to inform doctrinal standards): to deny patent protection for a new invention only when the invention would have been forthcoming (at about the same time) even without patent protection, *i.e.*, when patent protection was not needed to induce its emergence.[10] Moreover, like the word "obvious" in one understanding, what protection may be needed to induce the invention plausibly depends on the costs and uncer-

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[10] *See Graham v. John Deere Co.*, 383 U.S. 1, 11 (1966) ("The inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent."); *KSR*, 550 U.S. at 419 ("Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress. . . ."); *see generally* Abramowicz & Duffy, *supra*. Statutorily, this approach amounts to adding something like "if patent protection had been unavailable" as the missing "if" clause for the "would have been" phrase.

tainties of the work required for success. *See*, *e.g.*, Abramowicz & Duffy, *supra*, at 1613–14, 1655; William M. Landes & Richard A. Posner, *The Economic Structure of Intellectual Property Law* 304 (2003).

4. The definitional questions seem to bear materially on one issue central to Bristol-Myers' argument—whether the post-filing evidence of 2′-CDG's immediate and conclusive failure in animal testing is significant to assessing whether, before such testing, there truly was a reasonable expectation of relevant (human-therapeutic) success of 2′-CDG (and hence of entecavir). As a general evidentiary matter, it seems relevant to determining the reasonableness of any expectation before conducting a readily available animal test that the very first animal test immediately showed such toxicity that 2′-CDG has never since been tried in humans.[11] Even in the arena of busi-

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[11] *Cf., e.g.*, 22 Charles Alan Wright & Kenneth W. Graham, Jr., *Federal Practice & Procedure* § 5171, at 752–57 (2012) (experiments conducted after the event in question may be admitted to show what could have been done, what might have happened, to reveal the characteristics of a product or the dangers arising from it); *Burke v. Deere & Co.*, 6 F.3d 497, 505–06 (8th Cir. 1993) (accidents taking place after a manufacturer sold a specific item to the plaintiff admissible to determine the actual risk of harm posed by the defective product); *Rocky Mountain Helicopters, Inc. v. Bell Helicopters Textron*, 805 F.2d 907, 918 (10th Cir. 1986) (results of a post-accident stress test admissible in products liability trial, provided study redacted any evidence of a subsequent redesign); *Bailey v. Kawasaki-Kisen, K.K.*, 455 F.2d 392, 397–98 (5th Cir. 1972) (where individual was injured by a falling boom, evidence of the boom falling a second time was admissible to prove that the boom was in fact defective), abrogated in distinct respect (subsequent remedial measures) by Fed.

ness forecasts—where changes in the world over time can dramatically affect results—courts temper a great caution about hindsight bias with a recognition that "a gross disparity between prediction and fact" may be relevant to assessing the reasonableness of the prediction.[12] All the more so in the present context, which involves a general biological property (toxicity of a particular compound) that should be the same today as it will be next year. But whether this is a sensible analysis may well depend on precisely what "reasonable expectation" means in the present context.

I would grant rehearing en banc to enable a full exploration of these questions.

R. Evid. 407, as stated in *Rutledge v. Harley-Davidson Motor Co.*, 364 F. App'x 103, 106 (5th Cir. 2010).

[12] *Spitzberg v. Houston Am. Energy Corp.*, 758 F.3d 676, 691 (5th Cir. 2014) (a "gross disparity between prediction and fact" may form the basis for 10b-5 liability) (quoting *Lormand v. US Unwired, Inc.*, 565 F.3d 228, 248 n.13 (5th Cir. 2009)); *Marx v. Computer Scis. Corp.,* 507 F.2d 485, 489 (9th Cir. 1974); *G & M, Inc. v. Newbern*, 488 F.2d 742, 745–46 (9th Cir. 1973).