2013-1306

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRISTOL-MYERS SQUIBB COMPANY,

Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

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

BRISTOL-MYERS SQUIBB COMPANY'S COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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July 14, 2014

CERTIFICATE OF INTEREST

Counsel for Bristol-Myers Squibb Company certifies as follows:

1. The full name of every party or amicus represented by us is:

Bristol-Myers Squibb Company

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:

Not applicable.

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 us are:

None.

4. The names of all law firms and the partners or associates that appeared for the parties represented by us in the trial court, or are expected to appear in this Court, are:

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Dated: July 14, 2014

/s/ William F. Lee
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STATEMENT OF COUNSEL

Based on my professional judgment, I believe the panel decision is contrary to the following precedents of the Supreme Court and this Court: *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); *Graham v. John Deere Co.*, 383 U.S. 1 (1966); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354 (Fed. Cir. 2014); *In re Cyclobenzaprine*, 676 F.3d 1063 (Fed. Cir. 2012); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291 (Fed. Cir. 2011); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381 (Fed. Cir. 2004); *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963).

Dated: July 14, 2014 */s/ William F. Lee*
WILLIAM F. LEE

INTRODUCTION

The Supreme Court held in *Graham* that 35 U.S.C. § 103 requires an objective assessment of the "differences between the prior art and the claims at issue." 383 U.S. at 17. This Court has repeatedly and consistently held that later-discovered differences between the prior art and the claimed invention must be considered in making that assessment, consistent with the statutory mandate that obviousness depends upon the differences between the prior art and the claimed invention "as a whole," 35 U.S.C. § 103. *See Sanofi-Aventis*, 748 F.3d at 1360; *Genetics Inst.*, 655 F.3d at 1307; *Knoll*, 367 F.3d at 1385. The panel decision in

this case conflicts with this precedent by limiting its consideration of unexpected results to "the time of the invention," Op. 16, without taking into account the significant differences between the prior art and the claimed invention that were discovered shortly thereafter. This departure from *Graham* and this Court's prior decisions will create confusion in the trial courts and PTO and, for the first time, allow a holding of obviousness to rest on a false understanding of the differences between the prior art and the claimed invention. The panel compounded the error by improperly dismissing powerful objective evidence of nonobviousness, viewing only selected pieces of the evidence, and then only in isolation, and drawing rigid distinctions between "differences in degree" and "differences in kind." Only through these legal errors could the panel find a patent claim to a life-saving therapeutic compound obvious over two toxic prior art compounds. The Court should grant panel rehearing or rehearing en banc to correct these unwarranted and unauthorized reversals of precedent.

This case involves a claim to the new chemical compound entecavir, which is the active ingredient in BMS's hepatitis B drug Baraclude®. By any measure, entecavir is an exceptional compound. It is by far the most potent hepatitis B drug ever discovered, yet is exceptionally safe and avoids side effects and the problems of drug resistance common to other hepatitis B drugs. Those properties have made entecavir a commercial success, with billions of dollars in sales since its launch.

The panel held entecavir obvious over the prior art compound 2'-CDG based on a presumption that, in light of certain structural similarities between the two compounds, they would have similar properties. In fact, their properties are vastly different: Entecavir is a life-saving drug for millions of people suffering from hepatitis B, while 2'-CDG is highly toxic and thus has no therapeutic use.

This Court has never before held obvious a new chemical compound with such unexpected differences from the prior art. The panel did so here only through legal errors, two of which warrant rehearing given their implications beyond this case. *First*, the panel erroneously declined to consider the fundamental difference in toxicity between the claimed invention and prior art, reasoning that because 2'-CDG's toxicity was not discovered until shortly after entecavir's invention, a skilled artisan would have expected modifications to 2'-CDG to produce safe compounds. This refusal to consider the actual difference between the prior art and claimed invention not only conflicts with precedent but will have devastating consequences for drug discovery, where a compound's beneficial and nonobvious properties are often fully revealed only after years of study. It also leads to the perplexing result that the same claim considered obvious at one point in time based on incomplete information might become nonobvious the *later* an applicant files.

Second, the panel decision minimized the important role that objective indicia as a whole play in guarding against mistaken conclusions of obviousness.

Rather than considering the claimed invention's unique combination of properties—which are literally the difference between life and death for patients suffering from hepatitis B and have made entecavir a commercial success—the panel dismissed certain of entecavir's properties individually as mere "differences in degree" from the prior art. Op. 16. The panel's focus on only two discrete properties individually rather than the differences from the prior art as a whole is inconsistent with precedent and the realities of drug discovery, where the success of a new compound depends upon all of its properties together.

The Court should grant panel rehearing or rehearing en banc to correct the panel's two significant departures from precedent, which will have a dramatic impact on the future of drug discovery.

BACKGROUND

BMS owns U.S. Patent No. 5,206,244 ("the '244 patent"). Claim 8 of the '244 patent is specifically directed to the chemical compound entecavir, which is the active ingredient in BMS's hepatitis B drug Baraclude®. BMS sued Teva for infringement of the '244 patent after Teva filed an abbreviated new drug application seeking FDA approval to market a generic version of Baraclude®. After a bench trial, the district court held claim 8 obvious. A153. On June 12, 2014, a panel of this Court affirmed the district court's invalidity judgment.

Entecavir belongs to a class of compounds known as nucleoside analogs. Natural nucleosides are the building blocks of DNA and RNA. Nucleoside analogs mimic the structure of natural nucleosides, but can differ from those natural nucleosides in ways that interfere with the replication of viral DNA and make them potent antiviral compounds. A8(¶19); A1035(136:18-137:12). What makes nucleoside analogs effective antiviral agents, however, can also result in toxicity by interfering with the replication of human DNA. A2028(1:29-33) ("[F]ew [nucleoside analogs] have good activity against the virus without untoward side effects."). A great challenge in the field of nucleoside analog research therefore is to discover compounds that have a high degree of antiviral activity but little toxicity. That task is made more difficult by the fact that even small changes in structure are known to have a significant effect on a nucleoside analog's biological activity. A1204(805:10-15). Indeed, many nucleoside analogs that were initially believed to be promising antiviral compounds later proved toxic in further study. *See, e.g.*, A1208(821:6-16); A1256(1011:3-1012:8); A1341(1348:20-1349:2).

There are three broad classes of nucleoside analogs: furanosides, acyclics, and carbocyclics. A18(¶48). Entecavir is a carbocyclic. Although the FDA had approved several antiviral furanosides and acyclics at the time of entecavir's discovery in 1990, no carbocyclic had been approved for any purpose. A20(¶59). Even today, entecavir is the only carbocyclic approved for treatment of hepatitis B.

Although, even after several decades, research into carbocyclics had not resulted in any FDA-approved drugs, the panel concluded that "those of ordinary skill in the art would have selected 2'-CDG, a carbocyclic analog, as a lead compound for further development efforts." Op. 10-11. The chemical structure of entecavir differs from that of 2'-CDG by a single chemical group—a double-bonded carbon at the top of the carbocyclic ring. *See* Op. 6. But the two compounds have very different biological activity. While the panel relied on several studies predating BMS's discovery of entecavir that suggested that 2'-CDG appeared to be a promising antiviral compound, *see* Op. 4-6, 2'-CDG was soon after discovered to be highly toxic. Indeed, 2'-CDG is so toxic that scientists in one animal study from the early 1990s "never found a dose [of 2'-CDG] that wasn't toxic." A1255(1009:18-1010:9). 2'-CDG therefore has never been used in humans for any purpose. A1255(1010:12-17). Although 2'-CDG's toxicity was not fully appreciated at the time of entecavir's invention, it is an intrinsic property of the prior art that fundamentally distinguishes it from the claimed invention.

Having selected 2'-CDG as a lead compound, the panel then engaged in a multi-step analysis to choose the modifications to 2'-CDG needed to arrive at the chemical structure of entecavir. *See* Op. 9 (listing steps in analysis). After several steps to determine where 2'-CDG might be modified, the panel considered which chemical modifications a skilled artisan might make. That analysis focused on a

particular chemical modification found only in a single prior publication disclosing a compound known as Madhavan compound 30. Compound 30 had a double-bonded carbon group, or "methylene," attached at the top of the carbocyclic ring. A169; A1078(308:13-309:1). When that substituent group is added to the structure of 2'-CDG, the result is the chemical structure of entecavir. Op. 6, 11. Compound 30 was "[t]he most potent, but also the most toxic" of the compounds in the Madhavan reference. A2003. Madhavan disclosed another compound that lacked a methylene substitution that was "nearly as active and much less toxic." *Id.*

The panel nevertheless concluded that a skilled artisan would have had a reasonable expectation of success when modifying 2'-CDG to add a methylene group at the top of the carbocyclic ring, as found in Madhavan compound 30. Op. 14. Specifically, the panel presumed that the resulting compound would have properties similar to 2'-CDG because the addition of a methylene group was supposedly a small structural modification and the panel considered it "well settled that structurally similar compounds often have similar properties." *Id.* The panel did not consider 2'-CDG's high toxicity in assessing a reasonable expectation of success because that toxicity was not appreciated at the time of entecavir's discovery.

Although the panel acknowledged that unexpected differences between 2'-CDG and entecavir should "come into play in determining 'the ultimate question

of patentability,'" Op. 15, it never considered the fundamental difference between 2'-CDG and entecavir that is known today. Instead, the panel deferred to the district court's findings about what skilled artisans would have incorrectly thought about 2'-CDG's toxicity at the time of the invention. Op. 17 ("Thus, while the district court found that entecavir's *degree* of effectiveness was unexpected, it also noted that entecavir's 'effectiveness against hepatitis B without known toxicity issues' was '*not unexpected*' in light of the structurally similar 2'-CDG.").

ARGUMENT

I. UNDER SETTLED PRECEDENT, A LATER-DISCOVERED DIFFERENCE IN TOXICITY BETWEEN THE PRIOR ART AND THE CLAIMED INVENTION MUST BE CONSIDERED WHEN ASSESSING UNEXPECTED RESULTS.

The panel's determination of obviousness rested on the presumption that "structurally similar compounds often have similar properties." Op. 14. When applying that presumption, this Court has emphasized the need to consider *all* of the differences between the prior art and the claimed invention, even those differences that were not known at the time of the invention. Indeed, for a determination of obviousness that rests on the presumption that structurally similar compounds will have similar properties, there could be no stronger proof of nonobviousness than the fact that the supposedly similar compounds actually have vastly different properties. *See, e.g.*, *Papesch*, 315 F.2d at 391 ("An assumed similarity based on a comparison of formulae must give way to evidence that the

assumption is erroneous."). That is particularly true of differences in toxicity, which "would bear heavily" on the obviousness analysis. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013); *see also Takeda*, 492 F.3d at 1362 (holding that "any presumed expectation that [the prior art and the claimed invention] would share similar properties" is rebutted by evidence of differences in toxicity).

Here, the differences between entecavir and 2'-CDG are stark: Entecavir is a life-saving drug with exceptional safety, whereas 2'-CDG is so toxic it has never been used in humans. The panel nevertheless disregarded 2'-CDG's toxicity because it was not appreciated at the time of entecavir's invention. The panel instead limited its consideration of unexpected results to only those differences that would have been unexpected "at the time of the invention." Op. 16. That narrowed analysis made the presumption of success based on structural similarity effectively unrebuttable by ignoring the later-discovered unexpected result that defeats the presumption.

The panel's ruling directly conflicts with this Court's repeated holdings that later-discovered differences between the prior art and the claimed invention must be taken into account as unexpected results. *See, e.g.*, *Sanofi-Aventis*, 748 F.3d at 1360 ("[P]atentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest."); *Genetics*

Inst., 655 F.3d at 1307 ("Our law is equally clear that every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness."); *Knoll*, 367 F.3d at 1385 ("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.").

This Court's rule requiring consideration of later-discovered differences reflects the long-standing principle that "a compound and all of its properties are inseparable," *Papesch*, 315 F.2d at 391, and the statutory requirement that obviousness depends upon "the claimed invention as a whole," 35 U.S.C. § 103. *See, e.g.*, *Genetics Inst.*, 655 F.3d at 1307 ("Our case law is clear that the structure of a claimed compound and its properties are inseparable for purposes of § 103."); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination."); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) ("This court will not ignore a relevant property of a compound in the obviousness calculus.").

Indeed, *Graham* itself requires an objective analysis of the "differences between the prior art and the claims at issue," not an analysis skewed by

misconceptions as to what those differences are. 383 U.S. at 17. That is a sensible rule because consideration of all the differences between the claimed invention and the prior art—even differences that are subsequently discovered—is necessary to keep the obviousness analysis grounded in scientific reality and to ensure that the unpredictable nature of the art is taken into account.

This Court accordingly has recognized that subsequently discovered differences from the prior art are precisely the type of unexpected results that provide strong objective evidence of nonobviousness. *Sanofi-Aventis*, 748 F.3d at 1360 (explaining that unexpected "later-discovered benefits" of the claimed invention over the prior art properly supported a finding of no obviousness); *Genetics Inst.*, 655 F.3d at 1307 (upholding reliance on subsequently discovered unexpected results because "[r]elevant secondary considerations often are not manifest even until well after the issuance of a patent"); *Papesch*, 315 F.2d at 383, 391 (rejecting obviousness argument based on structural similarity where test results submitted during prosecution showing that the claimed invention had "completely dissimilar biological properties" from the asserted prior art). By rigidly applying the presumption that structurally similar compounds will have similar properties without taking into account the later-discovered difference in toxicity, the panel effectively constructed "a selective version of the facts relating to the objective considerations so as to confirm its hunch that the asserted claims

were obvious." *Cyclobenzaprine*, 676 F.3d at 1080. The panel instead should have taken into account the actual differences between the claimed invention and the prior art, as *Graham* and this Court's cases require.

Teva and the panel have suggested that BMS is advocating a per se rule that any unexpected properties make a new chemical compound nonobvious. Op. 15. But no such rule is needed to hold that, where later-discovered differences between the claimed invention and the prior art show that supposedly structurally similar compounds actually have fundamentally different properties, obviousness should not be found. Indeed, the differences here are precisely the type this Court has held sufficient to overcome a presumption based on structural similarity. *See Takeda*, 492 F.3d at 1362 (holding that "any presumed expectation that [the prior art and the claimed invention] would share similar properties" is rebutted by evidence of differences in toxicity). The only per se rule in this case is the panel's rigid new rule that subsequently discovered differences between the claimed invention and the prior art cannot be considered in assessing unexpected results. *KSR*, 550 U.S. at 419 ("[W]hen a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.").

Unless corrected, the panel's erroneous approach of limiting its consideration of unexpected results to only those properties that would have been unexpected at the time of the invention will have sweeping consequences because

"understanding of the full range of an invention is not always achieved at the time of filing the patent application." *Knoll*, 367 F.3d at 1385. That is particularly true in drug development—where it may take years of study to reveal all of a compound's benefits (or shortcomings). The Court should grant panel rehearing or rehearing en banc to correct the panel's legally erroneous approach of ignoring the actual differences between the claimed invention and the prior art.

II. IN A SIGNIFICANT DEPARTURE FROM PRECEDENT, THE PANEL INCORRECTLY ANALYZED THE OBJECTIVE INDICIA, BASED IN PART ON A RIGID DISTINCTION BETWEEN DIFFERENCES IN DEGREE AND KIND.

Graham emphasized the importance of objective indicia of nonobviousness "to guard against slipping into use of hindsight." 383 U.S. at 36 (internal quotation marks omitted); *see also KSR*, 550 U.S. at 421 (noting the "distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning"). Accordingly, this Court has repeatedly recognized that the objective indicia "may often be the most probative and cogent evidence of nonobviousness in the record." *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (internal quotation marks omitted); *Leo Pharm. Prods. Co. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) ("Objective indicia of nonobviousness play a critical role in the obviousness analysis."); *Cyclobenzaprine*, 676 F.3d at 1078 ("[*Graham*] did not characterize the objective factors as after-the-fact considerations or relegate them to 'secondary status.'").

The wisdom of that precedent is nowhere more apparent than in this case. Entecavir's exceptional properties and reception in the marketplace confirm that its invention was much more than just the result of ordinary skill. Entecavir is by far the most potent hepatitis B drug ever discovered. While other hepatitis B drugs require daily doses of 20-600 milligrams, entecavir is effective with as little as 0.5 milligrams per day. A1344(1358:20-1360:17); A2255; A2256. And yet entecavir remains exceptionally safe with minimal side effects. A50-51(¶¶140, 142); A66(¶182). Further, unlike other nucleoside analog treatments for hepatitis B that develop resistance at alarmingly high rates (up to 70%), only 1.2% of patients beginning treatment with entecavir will develop resistance even after six years. A49-50(¶¶137-138). Entecavir's combination of unique and unexpected properties has made it a commercial success, with billions of dollars in sales worldwide since 2005. A1323(1276:18-1277:16); A2257. By 2009, entecavir became the most prescribed hepatitis B drug and since then has maintained roughly the same market share even as new drugs have come to market. A52-53(¶147).

The panel improperly minimized the significance of these objective indicia in an analysis that has far-reaching implications for other cases. Among other things, the panel relied on a rigid distinction between "differences in degree" and "differences in kind" to dismiss entecavir's exceptional potency and safety. Op. 16-17. But it is hardly a "difference of degree" that, unlike entecavir, the way 2'-

CDG works against hepatitis B would kill the patient too. The panel's decision thus extends the concept of "differences in degree" far beyond prior cases.[1]

Further, because a drug's therapeutic properties are all intertwined and necessary for a successful invention, it was error to dismiss entecavir's properties one by one instead of considering its unique *combination* of properties. Indeed, the objective indicia cannot guard against hindsight unless measured against the success actually achieved by the invention. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("success was finding a compound that had high activity, few side effects, and lacked toxicity," rather than a compound that merely had activity); *see also Institut Pasteur*, 738 F.3d at 1346 (success is "the highly desired goal" achieved by the claimed invention, not some "less challenging but also less worthwhile pursuit").

From any vantage point, entecavir is a safe, effective, and highly successful drug. If those objective considerations are insufficient for patentability, there could hardly be any new drug for which the objective indicia will be a meaningful safeguard against erroneous conclusions of obviousness.

CONCLUSION

The Court should grant panel rehearing or rehearing en banc.

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[1] The panel acknowledged entecavir's unexpected high genetic barrier to resistance, but dismissed it as "properly credited" by the district court (Op. 17)—even though the panel separately recognized that the district court's analysis on the point was legally flawed (Op. 18-19).

Respectfully submitted,

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July 14, 2014

CERTIFICATE OF SERVICE

I hereby certify that I filed the foregoing Bristol-Myers Squibb Company's Combined Petition for Panel Rehearing and Rehearing En Banc with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system this 14th day of July, 2014, and served a copy on counsel of record by the CM/ECF system.

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July 14, 2014

CERTIFICATE OF COMPLIANCE

Counsel for Bristol-Myers Squibb Company certifies that:

1. The brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 40(b) because exclusive of the exempted portions it does not exceed 15 double-spaced pages.

2. The brief 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) because it has been prepared using Microsoft Word 2010 in a proportionally spaced typeface: Times New Roman, font size 14 point.

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July 14, 2014

ADDENDUM

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.

Decided: June 12, 2014

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

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Before PROST,[*] *Chief Judge*, PLAGER and CHEN, *Circuit Judges*.

CHEN, *Circuit Judge*.

This patent infringement case concerns a drug for the treatment of hepatitis B. After a four-day bench trial, the United States District Court for the District of Delaware found claim 8 of U.S. Patent No. 5,206,244 ('244 patent) invalid as obvious. We affirm the district court's invalidity judgment for the reasons that follow.

I.

Appellant Bristol-Myers Squibb Co. (BMS) owns the '244 patent. Claim 8 of the '244 patent is directed to a nucleoside analog composed of two regions: a carbocyclic ring and a guanine base. Nucleoside analogs are man-made compounds designed to mimic the activity of natural nucleosides, the building blocks of DNA and RNA. These compounds are modified slightly from their natural counterparts to interfere with the replication of viral DNA—which means that they can serve as possible antiviral compounds. Claim 8 covers one such compound, entecavir. BMS markets entecavir as a treatment for hepatitis B under the trade name Baraclude®.

Entecavir is a modified version of the natural nucleoside 2′-deoxyguanosine (deoxyguanosine). Entecavir is structurally identical to deoxyguanosine except for one difference: it has a carbon-carbon double bond (also

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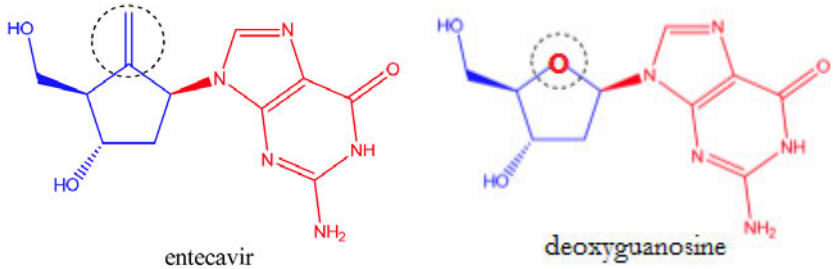
[*] Sharon Prost assumed the position of Chief Judge on May 31, 2014.

known as an exocyclic methylene group) at the 5' position of the carbocyclic ring where deoxyguanosine has an oxygen atom.

The chemical structures of entecavir and deoxyguanosine are illustrated below:



Appellant's Br. 8; *see also* J.A. 11.

The structures referenced throughout this opinion include a "carbocyclic ring" of carbon atoms, which is illustrated above as the pentagonal structure at the left of each diagram, and a nucleoside base, which is illustrated above as the double ring structure to the right. In both figures above, the nucleoside base is guanine.

Entecavir is an effective treatment for hepatitis B. The drug is generally accepted as a safe drug, with a broad therapeutic window for treatment, providing for a wide gap between low doses of the drug that are effective against disease and the high doses that could cause unwanted toxicity. It also has a high genetic barrier to resistance such that, if they have not previously received a nucleoside-based treatment, few patients treated with entecavir develop drug resistance to it.

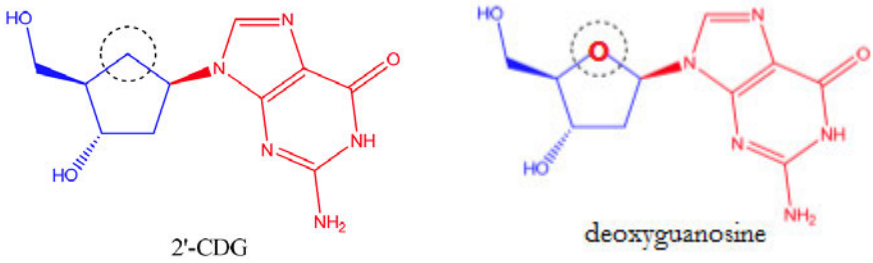
The appellee, Teva Pharmaceuticals USA, Inc. (Teva), filed an abbreviated new drug application (ANDA) for a generic version of entecavir. In support of its ANDA, Teva filed "Paragraph IV" certifications, alleging that its generic products would not infringe the '244 patent,

and/or that the patent was invalid or unenforceable. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

BMS sued Teva for patent infringement, claiming that Teva's ANDA filing infringed the '244 patent. *See* 35 U.S.C. § 271(e)(2). At trial, the parties narrowed the issues to obviousness and inequitable conduct.[1] Teva's obviousness argument focused on the selection of 2′-CDG as a lead compound from the prior art.

A.

2′-CDG is a potent antiviral carbocyclic nucleoside analog that is structurally similar to the natural nucleoside deoxyguanosine, differing only in that it replaces an oxygen atom with a carbon atom at the 5' position. The following illustrations compare the chemical structures of 2′-CDG and deoxyguanosine.



Appellant's Br. 14; *see also* J.A. 11, 23.

The earliest priority date for the '244 patent is the date that BMS filed the application, October 18, 1990. 2′-CDG's synthesis was first published in the *Journal of Medicinal Chemistry* in 1984 by Dr. Y. Fulmer Shealy (the

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[1] The district court found that Teva did not demonstrate by clear and convincing evidence that the inventor and prosecuting attorneys committed inequitable conduct. Teva does not raise the inequitable conduct issue on appeal.

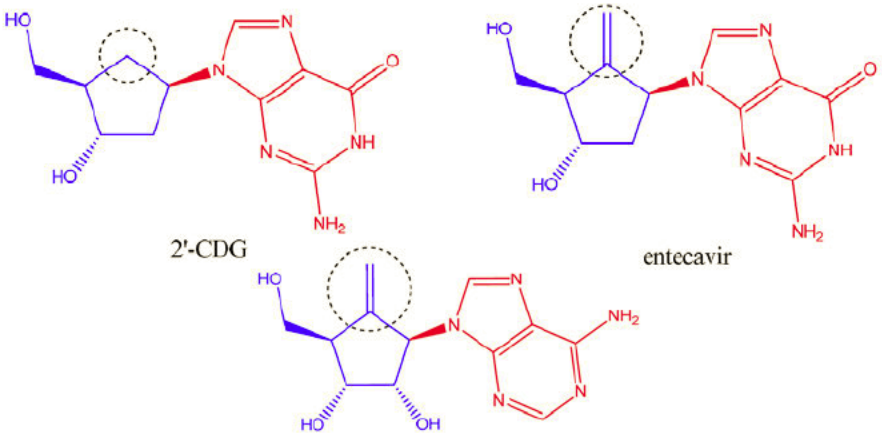
Shealy reference) of the Southern Research Institute (the SRI). The Shealy reference taught that 2′-CDG exhibited better *in vitro* antiviral activity against the herpes virus than the FDA-approved best-selling drug at the time, Ara-A. Dr. Shealy obtained a patent for 2′-CDG and other related compounds, stating that they were useful in the treatment of viral infections. Subsequent research on 2′-CDG by Dr. Shealy showed *in vivo* activity against herpes viruses.

After the Shealy reference was published, other researchers soon began working with 2′-CDG as an antiviral, including scientists at SRI, Mount Sinai School of Medicine, GlaxoSmithKline (Glaxo), and other institutions. In 1989, Dr. J.A. Montgomery of SRI published an article summarizing the state of antiviral research at the time and reported that 2′-CDG was "[b]y far the most promising" antiviral against herpes. J.A. 2148. The Montgomery reference also taught that 2′-CDG was five to six times more potent than one of the leading drugs on the market, acyclovir. Teva's expert, Dr. Heathcock, stated that the Montgomery reference was a "lamp post that really illuminate[d] 2′-CDG as … a very exciting lead compound to work from," and other chemists, during the relevant time period, were using 2′-CDG as a lead compound. J.A. 27. BMS's expert, Dr. Schneller, conceded that he did not "completely disagree" with Dr. Heathcock's opinion. J.A. 27-28. In fact, Dr. Schneller himself published research investigating antiviral activity of carbocyclics, including 2′-CDG, and cited to Dr. Shealy's article, noting the significant antiviral activity of 2′-CDG.

Also in 1989, Peter M. Price and other researchers with the Mount Sinai School of Medicine published the results of testing 2′-CDG against hepatitis (the Price reference). The Price reference disclosed that 2′-CDG showed "excellent activity" against the hepatitis B virus "with as little as 25 ng of 2′-CDG per ml" resulting in the "almost complete disappearance of replicating" hepatitis

B virus. J.A. 2086. The Price reference also taught that 2′-CDG was "nontoxic in concentrations up to 200 times the minimum effective inhibitory concentration." *Id.* According to Teva's expert, Dr. Heathcock, the Price reference demonstrated that 2′-CDG "had a very good therapeutic window [because] [i]t was effective at a level, much lower than its toxic level." J.A. 1048.

While Shealy, Montgomery, Price, and others studied 2′-CDG, a group of medicinal chemists at Syntex published antiviral studies on another nucleoside analog composed of a carbocyclic ring and adenosine base. J.A. 2001. The Madhavan reference disclosed that the substitution of an exocyclic methylene (carbon-to-carbon double bond) for the oxygen atom at the 5' position on the carbocyclic ring on nucleoside aristeromycin led to a nucleoside analog (Madhavan 30) with significantly superior antiviral properties. This exocyclic methylene substitution is the same modification at the same location made to 2′-CDG to form entecavir. The following illustrations compare the chemical structures of 2′-CDG, entecavir, and Madhavan 30.



Appellant's Br. 8, 14, 15.

According to BMS's inventor, Dr. Zahler, he was aware of the Madhavan reference before conceiving entecavir and testified that BMS submitted it to the USPTO as the "most relevant" piece of prior art in the '244 patent application. J.A. 1078, 1215, 1223. But BMS did not submit 2′-CDG as prior art to the USPTO.

B.

After a bench trial, the district court found that at the time of BMS's invention, 2′-CDG was a lead compound for the development of antiviral drugs. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 923 F. Supp. 2d 602, 665 (D. Del. 2013). Based on (1) the structural similarity between entecavir and 2′-CDG, (2) the teachings of the Madhavan reference, (3) the finding that the exocyclic methylene substitution would be a "small, conservative change[]"and (4) the "totality of the prior art" on 2′-CDG, the district court found that a skilled artisan would have been motivated to substitute an exocyclic methylene group at the 5' position of 2′-CDG, with a reasonable expectation of success of creating a compound with beneficial antiviral properties. *Id.* at 669, 675.

The district court also analyzed secondary considerations of nonobviousness. Although the court found that some of these considerations—commercial success, long-felt need, and evidence of unexpected properties—cut in favor of nonobviousness, the court ultimately concluded that Teva proved by clear and convincing evidence that claim 8 would have been obvious. *Id.* at 696. As a result, the district court entered judgment in favor of Teva. *Id.* BMS appeals the district court's invalidity finding. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II.

The only issue for our review is the district court's obviousness ruling. Obviousness is a question of law with underlying factual findings. *Honeywell Int'l, Inc. v.*

United States, 609 F.3d 1292, 1297 (Fed. Cir. 2010). We review the conclusion of obviousness *de novo*, and the trial court's factual findings for clear error. *Id.*

Obviousness requires assessing (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art." (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of nonobviousness such as "commercial success, long-felt but unsolved needs, failure of others, etc." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A party seeking to invalidate a patent as obvious must demonstrate "'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). Generally, an obviousness inquiry concerning such "known compounds" focuses on the identity of a "lead compound." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

A lead compound is a compound in the prior art that would be "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art. "[I]t is sufficient to show that the claimed and prior art

compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1293 (Fed. Cir. 2012) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). Whether a lead compound and a claimed compound have a sufficiently close relationship frequently turns on their "structural similarities and differences." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

Based on the prior art and testimony, the district court properly found strong evidence of obviousness, because the record shows that a skilled artisan would have selected 2′-CDG as a lead compound and made the minor modification to arrive at entecavir. Moreover, we see no clear error in the district court's fact findings regarding evidence of secondary considerations of nonobviousness.

A.

BMS attacks the lower court's obviousness determination by contending that a skilled artisan would have had to make too many decisions to arrive at entecavir. Those decisions include selecting (1) the class of nucleoside analog compounds, (2) 2′-CDG as a lead compound from the class of carbocyclics, (3) the carbocyclic ring or guanine base of 2′-CDG for modification, (4) the 2' or 5' position on the carbocyclic ring, (5) the specific chemical element on the 5' position (carbon), and (6) the type of carbon to carbon bond (single or double). We conclude that the district court's analysis is well supported.

During the relevant time period in the late 1980s, carbocyclic analogs were generating a great deal of interest among researchers searching for compounds with antiviral activity. Both parties' experts agree on that point. Several research institutions—including Glaxo, Syntex, Abbott Laboratories, and SRI— investigated and

published on antiviral activity of carbocyclic nucleosides. Thus, the district court had sufficient evidence to conclude that one of ordinary skill in the art during the relevant time period would have studied carbocyclic analogs "as a promising area" for antiviral drug discovery. J.A. 97.

Of the carbocyclic analogs on which researchers focused in the late 1980s, 2′-CDG was a "natural choice for further development." *Altana*, 566 F.3d at 1008. The district court observed, based on BMS's expert's own testimony, that "medicinal chemists during the relevant time frame *were actually treating and using* 2′-CDG as a lead compound" in the search for new antivirals at the time. J.A. 97 (emphasis in original). The Shealy, Montgomery, and Price references collectively reinforce that understanding of 2′-CDG.

BMS challenges the selection of 2′-CDG as a lead compound because it was discovered to be toxic in the 1990s. However, at the time of entecavir's invention, the Price reference showed that 2′-CDG was generally understood to be safe and nontoxic, and other researchers were already using it as a lead compound. As the district court points out, in "October 1990, 2′-CDG was *not yet known* to have high toxicity," and BMS's expert, Dr. Schneller, agreed that researchers at the time treated 2′-CDG as a "promising compound." J.A. 104, 111 (emphasis in original). Therefore, we see no error in the selection of 2′-CDG as the lead compound here. *See Velander v. Garner*, 348 F.3d 1359, 1377 (Fed. Cir. 2003) ("Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art *at the time of invention*." (emphasis added) (citation omitted)); *see also Eisai*, 533 F.3d at 1359.

Accordingly, we therefore agree with the district court that those of ordinary skill in the art would have selected 2′-CDG, a carbocyclic analog, as a lead compound for further development efforts before BMS applied for the

'244 patent in October 1990. *See Daiichi*, 619 F.3d at 1354 (explaining that more than mere structural similarity must be identified as a reason to select a compound as a lead compound; "knowledge in the art of the functional properties and limitations of the prior art compounds" are also important to the analysis).[2]

After selecting a lead compound, both experts (Dr. Schneller and Dr. Heathcock) agreed that a chemist in drug development would seek to make small, conservative changes to that structure. In drug development, it is common to modify a lead compound in an effort to "obtain a compound with better activity." *Otsuka*, 678 F.3d at 1291 (quotation omitted).

With 2′-CDG as a lead compound, the record here amply supports the conclusion that one of ordinary skill in the art would have had a motivation to modify 2′-CDG's carbocyclic ring by substituting an exocyclic methylene group at the 5' position to make the patented compound, entecavir. *See Otsuka*, 678 F.3d at 1292; *see also Takeda*, 492 F.3d at 1357.

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[2] BMS asserts that the district court erroneously failed to consider other nucleoside analogs as potential lead compounds. We disagree. The district court assessed all three classes of nucleosides (furanosides, acyclics, and carbocyclics) but explained that the field for furanosides and acyclics, compared to carbocyclics, was "crowded" and "fairly well developed" to the point that one would have a "hard time finding [a furanoside or acyclic that] someone else hadn't already tried." J.A. 19, 94. This is in marked contrast to the "fertile" field of research in carbocyclics. *Id.*

In choosing whether to modify 2′-CDG's carbocyclic ring or its guanine base, BMS's expert, Dr. Schneller, initially testified that he would "retain the [carbocyclic] portion," J.A. 114, but he acknowledged on cross-examination that other chemists were making changes to the carbocyclic portion. JA 1307-08. Teva's expert, Dr. Heathcock, also testified that changing the carbocyclic portion resulted in greater activity than changes to the guanine ring. Accordingly, this was a natural decision because the goal was to develop antivirals with improved activity.

Unrefuted expert testimony also explained how the next obvious choice for modification would have been either the 2' or 5' position on the carbocyclic ring, because only at these locations could small changes easily be made to the molecule. Both experts agreed that a skilled artisan would focus on the smallest elements on the top row of the periodic table, including carbon and fluorine. For a specific element, BMS's expert, Dr. Schneller, testified in his deposition that he would "rule out everything but the carbon" and that carbon was "the only one that sticks out." J.A. 1304. Teva's expert, Dr. Heathcock, also explained that the choice to have an exocyclic methylene (carbon-to-carbon double bond) over a methyl group (carbon-to-carbon single bond) would be a more conservative choice, because a methyl group is bigger and longer than an exocyclic methylene group, and the easiest way to synthesize a methyl group would be to make methylene first. J.A. 117-118, 1053, 1306.

Futhermore, the Madhavan reference demonstrated that adding an exocyclic methylene group to a carbocyclic nucleoside analog can result in a lead compound with improved antiviral activity. Specifically, it teaches that aristeromycin and Madhavan 30 were two compounds that differed only in the presence of an exocyclic methylene substitution at the 5' position; that modification resulted in the formation of a much more potent antiviral.

Teva's expert, Dr. Heathcock, testified that the substitution was an "obvious modification" in light of the prior art "because there were other [antiviral] compounds like that that had already been made" and a chemist would expect the nucleoside analog "to have similar biological properties of [2′-]CDG itself, which were good properties." J.A. 44. During prosecution of the '244 patent, BMS presented the Madhavan reference as containing the closest piece of prior art to entecavir. BMS's expert, Dr. Schneller, does not directly state that entecavir was obvious. But, on cross examination, Dr. Schneller stated that the Madhavan reference "would not dissuade" a chemist from adding the exocyclic methylene to form an antiviral drug. And even though the Madhavan compound was more toxic than the underlying lead compound, aristeromycin, (which itself was cytotoxic), Dr. Schneller admitted that the combination of features reported in the Madhavan and Shealy references "could have led" a person of skill in the art to seek new antivirals. J.A. 1311-12.

Based on the record, we see no clear error in the district court's finding that the modification required to transform 2′-CDG into the structurally similar entecavir is a minor one: the addition of a single carbon atom to form an exocyclic methylene with the already-present carbon atom at the 5' position of the carbocyclic ring of 2′-CDG to create entecavir. *See supra* at 6. Upon selecting 2′-CDG as the lead compound, the steps of deciding which bond to modify and how to modify that bond "equate to a small, finite number of changes to try to [arrive at] the lead compound." J.A. 117. *See In re Cyclobenzaprine Hydrochloride Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) ("Evidence of obviousness . . . is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have

had a reason to select the route that produced the claimed invention.") (citations omitted).

Further, the skilled artisan's reasonable expectation of success is measured "as of the date of the invention." *Amgen Inc., v. Hoffman-LaRoche*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). The Madhavan reference's teachings of improved potency with an exocyclic methylene at the 5' position supports the expectation that the same substitution to 2′-CDG would reasonably lead to similar properties. As explained above, 2′-CDG and entecavir are very structurally similar, and it is well settled that structurally similar compounds often have similar properties. *See Takeda*, 492 F.3d at 1356; *Altana*, 566 F.3d at 1007; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("[T]he presumption [is] that similar compositions have similar properties.").

BMS fails to establish any clear error in the district court's factual determinations, which are based on the prior art and expert testimony. In light of those factual findings, we agree with the district court that Teva provided strong evidence of obviousness, given the use of 2′-CDG as a lead compound during the relevant time period, the "totality of the prior art," and the structural similarity between entecavir and 2′-CDG suggesting similar properties. J.A. 128, 131.

BMS also argues that a new chemical entity, as a matter of law, cannot be obvious when the claimed invention possesses unexpected properties. Specifically, BMS argues that the existence of unexpected properties forecloses a finding of a reasonable expectation of success. We have already rejected this argument *en banc* in *Dillon*, explaining that an unexpected result or property does not by itself support a finding of nonobviousness. *Dillon*, 919 F.2d at 693, 697. In *Dillon*, we held that the expected properties of a claimed compound may be sufficient to lead to a reasonable expectation of success in modifying a

prior art compound to make that claimed compound. *Id.* at 697.

As here, *Dillon*'s claimed compound demonstrated both expected and additional, unexpected properties. Those 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. *Id.* at 693. We therefore upheld the finding of obviousness despite Dillon's arguments of unexpected properties.

Contrary to BMS's argument, unexpected results do not *per se* defeat, or prevent, the finding that a modification to a lead compound will yield expected, beneficial properties.[3] Rather, as secondary considerations of nonobviousness, they come into play in determining "the ultimate question of patentability." *Dillon*, 919 F.2d at 692-93; *Procter & Gamble*, 566 F.3d at 997-98 (citing to *Dillon* and finding evidence of superior properties such as potency and safety that were "unexpected and could not have been predicted" could outweigh evidence of obviousness).

B.

Secondary considerations of nonobviousness "must always when present be considered," and can serve as an important check against hindsight bias. *See Cyclobenzaprine*, 676 F.3d at 1075-76, 1079 (quoting *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983)). While secondary considerations must be taken

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[3] We have held an invention to be obvious despite findings of unexpected results. *See, e.g.*, *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013); *Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1365, 1369-70 (Fed. Cir. 2012); *Pfizer*, 480 F.3d at 1372.

into account, they do not necessarily control the obviousness determination. *Pfizer*, 480 F.3d at 1372; *see also KSR*, 550 U.S. at 426. Here, the district court found evidence of some secondary considerations of nonobviousness, including commercial success, long-felt need, and unexpected results. On appeal, BMS focuses primarily on unexpected results.

i.

To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006); *see also Pfizer*, 480 F.3d at 1371. Unexpected properties, however, do not necessarily guarantee that a new compound is nonobvious. While a "marked superiority" in an expected property may be enough in some circumstances to render a compound patentable, a "mere difference in degree" is insufficient. *In re Papesch*, 315 F.2d 381, 392 (CCPA 1963); *In re Hoch*, 428 F.2d 1341, 1344 n.5 (CCPA 1970) (explaining that unexpected "differences in properties" can mean "significant difference in degree of the same property" amounting to a "marked superiority" for purposes of evaluating unexpected results) (quotation omitted).

And "differences in degree" of a known and expected property are not as persuasive in rebutting obviousness as differences in "kind"—i.e., a new property dissimilar to the known property. *Compare In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (finding evidence that the new drug was a *more* potent sedative and *stronger* anticholinergic effect than the prior art was insufficient to outweigh the evidence of obviousness), *with In re Albrecht*, 514 F.2d 1389, 1396 (CCPA 1975) (reversing an obviousness rejection based on evidence of additional antiviral activity

"totally dissimilar to any activity previously disclosed for prior art"). When assessing unexpected properties, therefore, we must evaluate the significance and "kind" of expected results along with the unexpected results. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, --- F.3d ---, 2014 WL 1394948, at *7 (Fed. Cir. Apr. 11, 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected."); *In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 1990) (finding claims obvious when "[patentee] has not shown that a significant aspect of his claimed invention is unexpected in light of the prior art").

ii.

BMS primarily relies on three contentions for unexpected properties: (1) high potency against hepatitis B, (2) a larger than expected therapeutic window, and (3) a high genetic barrier to resistance. J.A. 150-51. The antiviral activity of entecavir, however, was not entirely unexpected because, as the district court found, it was already known in the prior art that 2′-CDG was effective against hepatitis B. J.A. 150. Specifically, the Price reference suggested that the structurally similar entecavir would likely have excellent antiviral activity against hepatitis B because 2′-CDG already demonstrated "excellent activity" against the virus. J.A. 2086. Moreover, the Price reference also suggested—and Teva's expert, Dr. Heathcock, testified—that 2′-CDG was known to have a good therapeutic window. Thus, while the district court found that entecavir's *degree* of effectiveness was unexpected, it also noted that entecavir's "effectiveness against hepatitis B without known toxicity issues" was "*not unexpected*" in light of the structurally similar 2′-CDG. J.A. 150 (emphasis added). As for the high genetic barrier to resistance, the district court properly credited this attribute as an

unexpected property. All taken together, the district court found that the proffered evidence of unexpected properties provided "some support to BMS's argument as to nonobviousness," but did not find it sufficient. J.A. 151-53.

We give deference to a lower court's factual findings regarding evidence of secondary considerations. *See In re Inland Steel Co.*, 265 F.3d 1354, 1366 (Fed. Cir. 2001) ("An examination for unexpected results 'is a factual, evidentiary inquiry,' … and we give the [fact-finding tribunal] broad deference in its weighing of the evidence before it."); *Santarus, Inc. v. Par Pharma., Inc.*, 694 F.3d 1344, 1358 (Fed. Cir. 2012) ("The district court's findings of fact are entitled to deference, and [Patentee] failed to show that they are clearly erroneous.") (citation omitted). Accordingly, we defer to the district court's finding on unexpected results.

BMS's remaining arguments regarding unexpected results are that the district court committed legal error by (1) comparing entecavir to another hepatitis B drug on the market instead of the closest prior art, 2′-CDG; and (2) inappropriately looked to what the inventor knew at the time of the invention—instead of one of ordinary skill in the art—to determine what was expected. BMS is correct on both counts. *See Kao*, 441 F.3d at 970 (explaining that when unexpected results are used as evidence of patent's nonobviousness, results must be shown to be unexpected compared with closest prior art); *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (holding that "obviousness is determined entirely with reference to a hypothetical 'person having ordinary skill in the art'" and the "actual inventor's skill is irrelevant" to the obviousness inquiry) (emphasis omitted). However, both errors were harmless. 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." J.A. 150 (emphasis added). And regardless of what the district court determined the inventor may have known, the prior art, the trial record, and the 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.

iii.

As for BMS's arguments regarding evidence of commercial success and long-felt need, we find no clear error with the district court's factual findings. The district court found that Baraclude® achieved commercial success based on sales and market share, but it was "less dynamic" than BMS represented. J.A. 138. Baraclude®'s market share built up gradually over four years and it ultimately held onto the top spot for less than a year. Evidence also showed that two other competitors were able to gain market share more quickly at launch than Baraclude®. J.A. 54, 137. Even BMS's internal documents viewed Baraclude®'s market performance as "sub optimal." J.A. 136-38.

On long-felt need, three other drugs for treating hepatitis B were invented before the filing date of entecavir. J.A. 147. These three drugs also gained FDA approval before entecavir. Finally, entecavir's inventors did not know about its hepatitis B properties until four years after the filing date, and by then the first FDA-approved hepatitis B treatment was launched. J.A. 147-48. Therefore, we agree with the district court that the evidence of long-felt need is of limited value to BMS.

Finally, BMS argues that the district court improperly compared the weight of the different secondary considerations against each other when it summarized that the factors were "mixed." J.A. 152. We understand the district court to be noting that some categories of evidence simply were not as helpful to BMS's case as others. We

do not read the opinion as suggesting that unhelpful evidence somehow diminished the strength of the more persuasive forms of evidence.

III.

We agree with the factual findings on secondary considerations and find no clear error. As stated previously, we also agree with the district court's finding that the record demonstrates strong evidence of obviousness. After considering all of the findings for and against obviousness, as well as Teva's burden of proof, we see no basis to disturb the district court's ultimate legal conclusion, and we affirm the judgment that claim 8 of the '244 patent is invalid as obvious.

AFFIRMED

COSTS

No costs.