No. 2013-1306

In the United States Court of Appeals for the Federal Circuit

BRISTOL-MYERS SQUIBB COMPANY,
PLAINTIFF-APPELLANT

v.

TEVA PHARMACEUTICALS USA, INC.,
DEFENDANT-APPELLEE

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE, CASE NO. 10-805-CJB, HON. CHRISTOPHER J. BURKE, MAGISTRATE JUDGE, PRESIDING

BRIEF OF DEFENDANT-APPELLEE TEVA PHARMACEUTICALS USA, INC.

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CERTIFICATE OF INTEREST

Pursuant to Circuit Rule 47.4, undersigned counsel for Defendant-Appellee Teva Pharmaceuticals USA, Inc., certifies the following:

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

   Teva Pharmaceuticals USA, Inc.

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; the party named in the caption is the real party in interest.

3. All parent corporations and any publicly held companies that own 10% or more of the stock of any party represented by us are:

   Teva Pharmaceuticals USA, Inc. is an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. which is a publicly traded company.

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

   Winston & Strawn LLP (George C. Lombardi, Lynn MacDonald Ulrich, Ivan M. Poullaos, Julia Mano Johnson, William P. Ferranti, James M. Hilmert, John R. McNair, Elizabeth J. Thompson); Phillips, Goldman & Spence, P.A. (John C. Phillips, Jr., Megan C. Haney)

Dated: July 18, 2013

/s/ George C. Lombardi
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STATEMENT OF RELATED CASES

Like counsel for Plaintiff-Appellant Bristol-Myers Squibb Co. ("BMS"), counsel for Defendant-Appellee Teva Pharmaceuticals USA, Inc. ("Teva") are not aware of any related cases within the meaning of Fed. Cir. R. 47.5.

INTRODUCTION

The remarkable thing about this appeal is not that the district court invalidated BMS's claim for the chemical compound, entecavir. It is that BMS's case for validity did not even have the support of BMS's own expert. That is why BMS's lead argument on appeal asks this Court to stretch established principles of obviousness law past the breaking point. In particular, BMS contends that obviousness cannot be found *as a matter of law* if an invention has an unexpected property that is discovered years after the fact. This, however, is simply wrong. There is no case holding that a showing of unexpected results *per se* defeats the reasonable-expectation requirement. To the contrary, numerous decisions of this Court have found *both* unexpected results and obviousness. And 35 U.S.C. §103 (2006) asks whether the invention "would have been obvious *at the time [it] was made* to a person having ordinary skill in the art." (Emphasis added).

That is the question the district court asked here, and the undisputed facts gave one clear answer: Entecavir is *not* a sufficient advance over the prior art to merit patent protection. By 1989-1990, others had already invented a promising

and structurally similar compound, 2'-CDG—a potent antiviral. Entecavir results from adding a single carbon atom to 2'-CDG. Consistent with the prior art, the expert testimony, and evidence of what researchers were actually doing at the time, the district court correctly found that it would have been obvious for a person of ordinary skill in the art to make that modification—as had been done with promising results by scientists working with other compounds.

Notably, the PTO did not actually conclude otherwise. BMS neglects to mention this fact, but it withheld from the PTO the most significant prior art—2'-CDG. Notwithstanding the presumption of validity afforded issued patents, the PTO's judgment "may lose significant force" where it "did not have all material facts before it." *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2251 (2011). That is the case here—and, as the district court recognized, BMS's omission makes Teva's burden of proving invalidity "easier to sustain." *Id.*

What is more, rendering hollow BMS's cry of "hindsight," the key facts in this case had the support of *both* parties' experts. In particular, Dr. Schneller, BMS's expert, testified that researchers in the late 1980s were actually "treating 2'-CDG as a lead compound" and that the prior art presented 2'-CDG as a "most promising" compound for its antiviral activity. He agreed that the ordinary chemist would have been motivated to make a "conservative" substitution to 2'-CDG. And the "most conservative change" that he could think of—the "only one that

sticks out" to him—was the substitution of a single carbon atom. That, of course, is the precise substitution necessary to change 2'-CDG to entecavir. And the ordinary chemist would have placed a double-bonded carbon at the 5' position of 2'-CDG with a reasonable expectation that the resulting compound (entecavir) would have antiviral activity because that is precisely what others in the field were doing to nucleoside analogs.

Dr. Schneller agreed with this, too. He testified about prior art (Madhavan) that disclosed substituting a double-bonded carbon in the 5' position—the same substitution, in the same position, that if made to 2'-CDG would yield entecavir. This was the teaching disclosed to the PTO as the closest prior art, and Dr. Schneller acknowledged that it "could have led a person of skill in the art" to "combin[e] the features reported in Madhavan [*i.e.*, the carbon substitution] with those in Shealy [*i.e.*, 2'-CDG]." In fact, he admitted that Madhavan "would persuade" the medicinal chemist to do so. Teva's expert (and the prior art) agreed wholeheartedly.

Accordingly, as the district court concluded, "as to almost every significant portion of the *prima facie* 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. On cross-examination, Dr. Schneller was forced to concede the accuracy of many significant points that Teva sought to assert as to that *prima facie* case. The force of this evidence was clear, and it was convincing." A152. It is thus un-

derstandable to find BMS in this appeal ignoring, trying to cabin, and even running from its expert. But BMS tries to replace its missing expert with new, unsupported attorney argument about the prior art—and that is no basis for reversal.

Nor is reversal warranted by any objective indicia of nonobviousness. BMS challenges the district court's assessment of that evidence, but the district court carefully considered all of it—including the fact that entecavir joined a bevy of other compounds that had antiviral properties, and the concomitant lack of skepticism regarding entecavir. Viewing the objective indicia together with the other evidence as a whole, and highlighting "the significant force of Teva's *prima facie* case, and the fact that the PTO was not able to consider certain material prior art references," the district court correctly concluded that obviousness had been established by clear and convincing evidence.

This Court should reject BMS's proposal to rewrite the law of obviousness. And, because BMS cannot establish any clear error in the district court's well-supported findings of fact, including its assessment of the objective considerations, the judgment of invalidity should be affirmed.

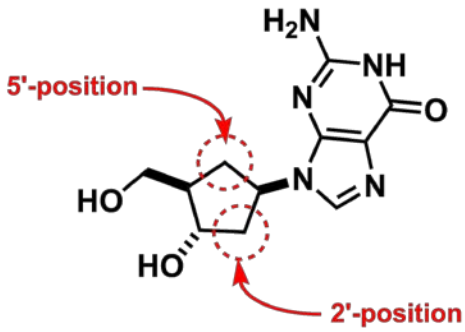
STATEMENT OF FACTS

BMS provides a selective account of the "facts" it thinks helpful—with little regard for the district court's findings, the record as a whole, or even the opinions of BMS's own experts. Below is the full tale.

A. Nucleoside analogs and entecavir

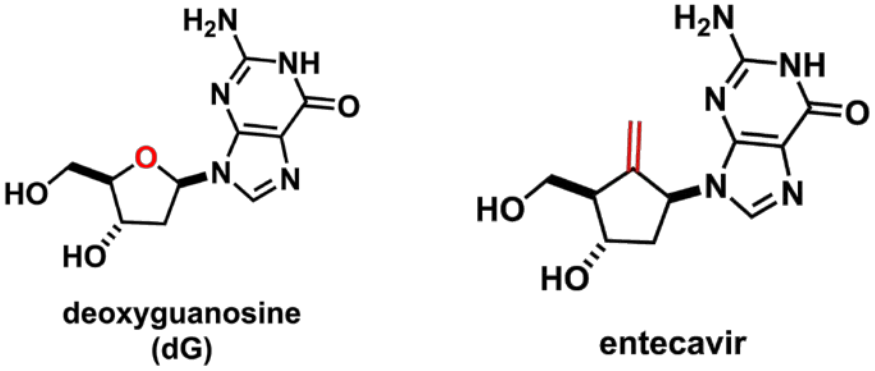
Entecavir is a carbocyclic nucleoside analog. A10. *Natural nucleosides* are part of the basic building blocks of DNA and RNA—and the starting point for antiviral research. They are simple chemical compounds that have a base portion and a sugar ring. A8. *Nucleoside analogs* are modified natural nucleosides. These compounds may interfere with the process by which a virus reproduces itself—which is why many antiviral drugs are nucleoside analogs. *Id.*

Two positions on the sugar ring are most important for present purposes: 2 prime (2') and 5 prime (5').



Nucleoside compounds can be broadly divided into those that have a hydroxyl group (-O-H) attached at the 2' position, and those that do not. Those *with* a hydroxyl group are the building blocks for RNA. Those without it—referred to as *2' deoxynucleosides*—are the building blocks for DNA. A9. *Carbocyclics* are nucleoside analogs that have a carbon atom (instead of an oxygen atom) at the 5' position. A20. (Note that the 5' position is sometimes referred to as 6', which means the same thing. A9 n.6.)

Entecavir is a carbocyclic version of the natural nucleoside 2' deoxyguanosine. That is, as illustrated below, entecavir differs from the natural compound in only one respect: the sugar ring of 2' deoxyguanosine has an oxygen atom at 5', while entecavir has a carbon-carbon double bond (also known as an *exocyclic methylene group*) at that position.



A10-11.

B. The '244 patent

Tracing back to an application filed on October 18, 1990 (A5), U.S. Patent 5,206,244 claims numerous nucleoside analogs that exhibit "[a]ntiviral activity," each of which has an exocyclic methylene group at the 5' position of the sugar portion. *See* A190-226; A9. At issue here is claim 8, which covers entecavir. A10.

Importantly, the '244 patent does *not* have a claim directed to a method of treating the hepatitis B virus ("HBV"). A1152 (598:13-17). Baraclude®, the commercial embodiment of entecavir, was approved by the FDA in 2005 to treat chronic HBV. A3-4. At the time the '244 patent was issued, however, entecavir

had not been tested to determine its activity against HBV. A72. The patent is based instead on *in vitro* test results showing activity against herpes family viruses and HIV; it states only that entecavir and the other claimed compounds "are also believed to be active" against several other viruses, including HBV. A11 (quoting A192 (3:67-4:41)). In other words, the claimed invention is *not* the use of entecavir to treat human patients for *any* disease (much less HBV in particular).

In addition, the inventors and prosecuting attorneys failed to disclose to the PTO the most similar prior art. Specifically, no one told the PTO about the nucleoside analog, 2'-CDG. A70; A153. In other, less similar applications, BMS cited 2'-CDG prior art and faced obviousness rejections based on it. *See* A77-78; A82; A1175-1176; A1184-1185. Teva is not pursuing its inequitable conduct defense on appeal. But, intentional or not, the failure to disclose 2'-CDG explains why the PTO granted this patent.

C. As the district court found, an ordinary medicinal chemist would have selected 2'-CDG as a lead compound in 1989-1990.

1. To discover new drugs in the late 1980s, "[t]he traditional approach—the easiest and probably the most common approach—was the modification of a known lead compound." A12. "A chemist utilizing this approach makes changes to an existing compound, known as a 'lead compound,' in an attempt to create a new compound with improved antiviral properties." *Id.* This approach follows

from the "tenet" that two compounds that are similar in structure can be expected to have similar activity. *Id.*

2. At the time of entecavir's invention, there were three classes of nucleoside analogs: furanosides, acyclics, and carbocyclics. A18. It was well-known that furanosides were capable of antiviral activity. A18-19. Similarly, scientists had been synthesizing acyclics for years. A19-20. As a result, the field for these nucleosides was "crowded" and "fairly well developed." *Id.* (quoting A1043 (168:13-20), A1196 (773:23-774:2)). A POSA would have had a "hard time finding [a furanoside or acyclic that] someone else hadn't already tried." A94 (quoting A1071 (278:22-23)).

In contrast, according to both parties' experts, the field of carbocyclics in the late 1980s was "fertile" with "growing interest." A21 (quoting A1043 (168:20-169:7) (citing A1293 (1154:5-1155:10)). In a 1989 article summarizing the antiviral research to date, a well-regarded chemist, Dr. Montgomery, stated that, "[b]y far the most active and selective agents are carbocyclic nucleoside analogs." A22 (quoting A2138). Teva's expert, Dr. Heathcock, explained that this statement would have served as a "pretty open invitation … to medicinal chemists to look at that class of compounds as leads." A22-23 (quoting A1048 (189:3-15)).

And chemists in the late 1980s were, in fact, regularly synthesizing carbocyclics. A20. For example, BMS's expert, Dr. Schneller, noted that in his lab, "it

was most of what we did." A20 (quoting A1303 (1194:4-11)); *see also* A1303 (1194:12-1195:8). Not only were chemists synthesizing carbocyclics, they were doing so with success. *See* A21-23. Indeed, antiviral activity with carbocyclics "appeared to be the rule rather than the exception." A21 (citation omitted).

Moreover, "in 1989, *BMS itself* was touting the promise exhibited by carbocyclics." A95. BMS reported in 1989 that its recently synthesized carbocyclic compound lobucavir had "excellent" antiviral activity, and was superior to a well-known acyclic, acyclovir. A22 (quoting A1226 (894:14-20)); *see also* A1293 (1156:14-20); A1227 (896:18-897:2).

Thus, the district court found, "the prior art in the relevant time period clearly pointed the skilled artisan to carbocyclics as a promising area for drug discovery." A97.

3. Within the field of carbocyclics, one promising compound that stood out was 2'-CDG. Invented by Dr. Shealy of the Southern Research Institute in 1984, 2'-CDG is a carbocyclic analog of the natural nucleoside 2' deoxyguanosine. A23. Dr. Shealy reported in a 1984 paper that 2'-CDG had "excellent activity," "high potency," and better antiviral activity *in vitro* than Ara-A—an FDA-approved treatment for herpes. A24 (quoting A2072) (citing A1045 (176:15-22)). In 1985, Dr. Shealy obtained U.S. Patent No. 4,543,255 claiming 2'-CDG. A24 (citing A2077-2085). Following the issuance of that patent, Dr. Shealy published

another article identifying 2'-CDG as a compound with *in vivo* activity. A25 (citing A2066-2070).

2'-CDG was not only singled out as a promising compound by its inventors; others in the field recognized it as a potent antiviral. For example, in one 1986 article (Marquez), the authors reported that 2'-CDG showed antiviral activity against HSV-1, and was more potent against HSV-2 than other carbocyclic nucleosides. A25 (citing A2109-2110). Additionally, in 1989, Dr. Peter Price of the Mount Sinai School of Medicine published a paper identifying 2'-CDG as having excellent activity against HBV, and a good therapeutic window due to its lack of toxicity. A26 (quoting A2086, A1048 (187:21-24)).

4. It is undisputed that those in the field also identified and used 2'-CDG as a lead compound at this time. In 1987, Glaxo scientists published an article reporting their own synthesis of 2'-CDG and its "high levels of selective antiviral activity." A28 (quoting A4020). Dr. Heathcock testified that this was "evidence that Glaxo had selected CDG as a lead structure to work from." *Id.* (quoting A1050 (194:3-10)). BMS's expert agreed. A27-28. The following year, the Glaxo scientists published a paper detailing their creation of a new compound with "extremely high levels of activity": using 2'-CDG as their lead, they had added a fluorine atom to the 2' position of the sugar portion. A28-29 (quoting A2090) (citing A2090-2092, A1050-1051, A1070).

In 1989, Dr. Montgomery published a paper that was "a lamp post that really illuminated 2'-CDG as a very exciting lead compound to work from." A27 (quoting A1049 (191:5-10)) (alteration marks omitted). Dr. Montgomery identified 2'-CDG as a promising lead compound. A27 ("By far the most promising carbocyclic purine nucleosides for the treatment of herpes infections are in the 2'-deoxyribo series ... Of these the most likely compounds appear to be the 2'-deoxyguanosine analog (CDG, 32) and its prodrug forms.") (quoting A2148). He also flagged that 2'-CDG was "five to six times as potent as acyclovir," the gold standard for antiviral compounds. A27 (quoting A1299 (1181:10-15)).

Even BMS used 2'-CDG as a lead compound in 1989. A120-121. BMS also included 2'-CDG as one of only two non-BMS compounds to validate the computer modeling that led to the synthesis of entecavir. A15; A1142.

Although 2'-CDG was eventually discovered to be highly toxic, this was not known in 1990. A30-33. To the contrary, in 1989, 2'-CDG was reported to be "nontoxic in concentrations up to 200 times the minimum effective inhibitory concentration." A33 (quoting A2086). Even BMS's expert witness, Dr. Tennant, who would later publish on 2'-CDG's toxicity, confirmed that when he started his testing in the 1990s, he was "absolutely not aware" of any toxicity associated with 2'-CDG. A33 (quoting A1258-1259 (1022:16-1023:6)). Nor would toxicity necessarily have precluded the use of 2'-CDG as a lead compound. *See* A34; A42;

A106-107 & n.23. Thus, as acknowledged in a 1997 paper in *Current Pharmaceutical Design*, 2'-CDG "played a pivotal role in providing a template for the development of carbocyclic nucleoside analogue programmes." A30 (quoting A4038).

D. The district court found that the prior art would have motivated an ordinary medicinal chemist to modify 2'-CDG by substituting a double-bonded carbon at the 5' position—with the expectation that the resulting compound could be readily synthesized and would have antiviral activity.

1. In agreement with both parties' experts, the district court found that, upon selecting 2'-CDG as a lead compound, an ordinary medicinal chemist would have pursued obvious, "conservative" changes. A37.

That meant modifying the carbocyclic ring because modifying the guanine base on acyclic compounds had demonstrated "a substantial *loss* of antiviral potency," resulting in compounds that "were at least 10-fold less active." *Id.* (quoting A2010, A1052 (203:6-204:9)) (emphasis added). As Dr. Heathcock testified, this would have informed the POSA that "you don't want to mess with the guanine." A1052 (204:3-9). In marked contrast, the prior art pointed to *increased* antiviral activity following changes to the carbocyclic ring. A37 (citing A1307-1308).

2. For a POSA focused on modification of the carbocyclic ring, there were only two good, conservative options—the 2' position and the 5' position. Because the 2' and 5' positions solely contain hydrogen atoms, they would have been obvious locations for modification. A37-38. Dr. Heathcock so opined, this is

reflected in the prior art, and the district court so found. *See* A39; A115 & n.28; A2091 (compound 8); A2001-2002 (compounds 10, 24, 30). In contrast, the 3' and 4' positions contain hydroxyl and hydroxymethyl groups that "the biochemical machinery is probably recognizing," which would have resulted in less conservative changes. A37-38 (quoting A1051-1052 (201:20-202:4)). No expert testified otherwise. A115 & n.28.

3. Both sides' experts also agreed that, in determining what change to make to the 2' or 5' positions, a skilled artisan would look first to the periodic table. A38; A116. In fact, Dr. Schneller testified that "you almost have to." A116-117 (quoting A1303 (1196:22-1197:9). And the POSA would have focused on the top row because these elements "have the smallest surface area and they make the short[est] test bonds when they are joined to something else." A38 (quoting A1052 (205:9-16)).

Looking to the eight elements in the top row, the experts agreed that the POSA would have avoided lithium, beryllium, boron, and neon because they are either too toxic, too reactive, or not reactive at all. *Id*. Looking to the remaining four elements, the POSA would have focused on carbon or fluorine because those elements "would not change the physical properties as much" as nitrogen and oxygen and "would be expected to give stable compounds that aren't much bigger than what you're starting with." *Id.* (quoting A2053 (206:8-12)).

BMS's expert, Dr. Schneller, even testified that he would "rule out everything but the carbon" and that the carbon was the "only one that sticks out" to him. A117 (quoting A1304-1305 (1200:7-14, 1203:1-6)).

4. Focusing on carbon, the POSA would have added a double carbon bond (exocyclic methylene) rather than a single carbon (methyl group). A39. This is because a double carbon bond is shorter and does not result in the addition of hydrogen atoms to the molecule; it thus would not "increase[] the surface area and volume" of the molecule as much. *Id.* (quoting A1053 (208:3-11)). Adding a single carbon methyl group (CH_3) would have been a less conservative change. *See* A39-40 (citing, *inter alia*, A1053 (208:3-209:1, 7-13), A1305 (1204:15-18), A1306 (1206:23-1207:4)).

And, as with the choice of lead compound, this is what medicinal chemists in the late 1980s were actually doing—*i.e.*, adding exocyclic methylene groups to nucleoside analogs. They added them to the 2' position, with promising results. *See* A40-41 (at least two such analogs exhibited potent antiviral activity) (citing A2008, A2024-2025). They also added them to the 5' position. In a 1988 article, chemists at Syntex ("the Madhavan group") added an exocyclic methylene group to aristeromycin—the carbocyclic analog of the natural nucleoside adenosine. A41 (discussing A2001-2003). This compound, known as "Madhavan 30," was found to have antiviral activity against herpes and other viruses. *Id.* (citing A1313). Ad-

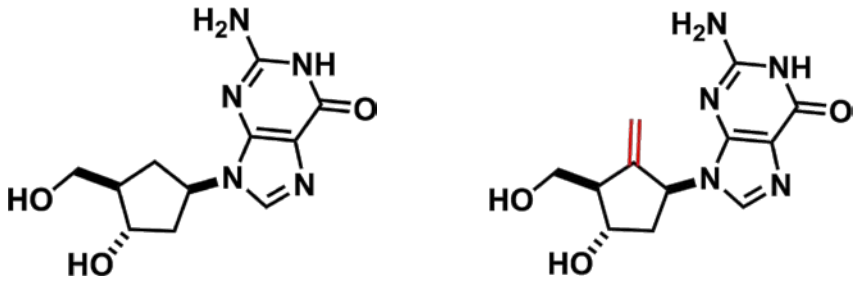
ditionally, it was the most potent compound the Madhavan group synthesized. *Id*. "Accordingly, an ordinary medicinal chemist would have had reason to combine Madhavan 30 and 2'-CDG by substituting an exocyclic methylene group at the 5 prime position of 2'-CDG." A44. In fact, omitting 2'-CDG, BMS disclosed Madhavan to the PTO as the closest prior art. A168-169.

Madhavan 30 was toxic, but this would not have deterred a POSA from substituting an exocyclic methylene group at the 5' position of 2'-CDG because Madhavan 30 involved the base adenine, not guanine. A41-42 (quoting A1055 (214:24-215:9)). In addition, Madhavan 30 was derived from aristeromycin, which was already known to be cytotoxic. A42 (citing A1055 (216:2-4)); A1314 (1240:13-15)). It was unknown whether Madhavan 30's toxicity was due to the natural properties of the lead compound, or the addition of the exocyclic methylene group. A41-42 (quoting A1055 (214:24-215:9)). And in any event, toxicity data in general would not have deterred a POSA from "making more compounds in the area to investigate further." A42 (quoting A1129 (508:8-19)).

Again, BMS's expert agreed. During his direct examination, Dr. Schneller contradicted his own written report and testified that a POSA "would not have been motivated to combine" 2'-CDG and Madhavan 30; it would have been "out of the question," he said. A43. On cross-examination, however, Dr. Schneller changed his tune (again). He admitted that Madhavan "*would persuade*" a medici-

nal chemist to add an exocyclic methylene group to the 5' position. *See* A42-43 (quoting and adding emphasis to A1311 (1228:19-1229:18)). He also admitted that his statements on direct examination were in direct conflict with those he made during his deposition, in his expert report, and on cross-examination—and that those other statements were truthful. A44 (citing A1311-1312). This testimony and those prior statements, which the district court credited, were consistent with the undisputed fact that researchers were actually making this modification to nucleoside compounds.

5. It is also undisputed that 2'-CDG and entecavir are structurally similar. A35. The only difference is the exocyclic methylene double carbon bond at the 5' position of entecavir:



A34. Based on this structural similarity, a POSA would have expected entecavir to have "similar biological properties to CDG itself." A45-46 (quoting A1056 (219:10-18)); *see also* A128; A1058 (226:18-24). Because 2'-CDG was known to have potent antiviral activity—*including against HBV*—an ordinary medicinal

chemist would have had a reasonable expectation of success that entecavir, too, would have those properties. A46 (citing A1058 (229:4-19)). A POSA also would have been heartened by prior art reflecting that other nucleoside analogs containing exocyclic methylene groups had shown potent antiviral activity. *See* A45-46; A1056 (219:13-18); A1058 (226:15-24).

6. Nor is there any dispute in this appeal that a POSA would have anticipated no trouble synthesizing entecavir. As the district court found, "synthetic organic chemistry is the stock and trade of a medicinal chemist," and thus "an ordinary medicinal chemist would have been able to synthesize entecavir after having conceived of it." A47 (internal quotation marks omitted).

E. Real-world evidence showed better than expected results for entecavir—but no failure of others or skepticism about this invention, which was the *fourth* nucleoside analog found during this period and later approved for treating HBV.

1. No skepticism surrounded entecavir. Due to entecavir's promising *in vitro* data against HBV, Teva's expert Dr. Thio explained that, "if anything, people should have been optimistic." A69 (quoting A1119 (467:2-7)). And they were. *See* A68-69. BMS's expert Dr. Gish testified that he and others were skeptical that entecavir could control HBV as a monotherapy—but Dr. Gish provided no detail as to these "others," and BMS could not corroborate Dr. Gish's testimony. *See* A67-68; A140. Further, Dr. Gish acknowledged that he gave BMS the green light to pursue FDA approval based on entecavir's promising *in vitro* data. A69; A1361

(1426:6-18). As the district court concluded, "[t]he sum total of the evidence regarding skepticism was … particularly thin." A140.

2. BMS's evidence of "failure of others" was similarly unpersuasive. A145. There was no failure of others to synthesize nucleoside analogs capable of antiviral activity or of treating HBV. A142-145. Rather, the "nucleoside analog field [was] a fruitful area for hepatitis B research." A55. Dr. Gish referred to the field as "dynamic," stating that 1998-2008 was a time of "huge change" as *five* different oral nucleoside analogs were FDA-approved to treat HBV. A144 (quoting A1357 (1413:4-14), A1362 (1431:5-11)). Dr. Thio similarly testified to an "explosion" of HBV treatments in a "relatively short period of time." *Id.* (quoting A1107 (420:23-421:1)). It was a time of "[s]ignificant advances" and "substantial progress." A144-145 (quoting A4002, A4010).

3. This is also reflected in the district court's findings regarding long-felt unmet need: Although one existed, by 1990, three *other* HBV treatments had already been invented. A147. Adefovir and tenofovir were invented in 1986, and lamivudine was invented by 1989. *See* A61-63. These treatments, too, were used "with significant success to treat hepatitis B." A147.

4. Entecavir's "unexpected" results were, at best, a matter of degree. It was *expected* in 1990 that entecavir would have antiviral activity against HBV. A47; A149. Although the district court found that entecavir's *in vitro* potency

"provides some support to BMS's argument as to nonobviousness" (A152), 2'-CDG was known prior to 1990 to have high *in vitro* potency against HBV (A26).

Similarly, entecavir's safety profile would have been expected based on what was then known about 2'-CDG. *See* A30-34 (2'-CDG not known to be toxic before 1990); A26 (prior art reported 2'-CDG "nontoxic in concentrations up to 200 times the minimum effective inhibitory concentration").

BMS failed to present any evidence that, in 1990, entecavir would not have been expected to have a high genetic barrier to resistance.

5. Baraclude, the commercial embodiment of claim 8 of the '244 patent, was not a particularly "dynamic" commercial success. A138. At all times that Baraclude has been available, well over half the prescriptions written for the treatment of HBV were written for something else. A53. Even four years after its launch, Baraclude had only 36% of the HBV market. A52-53. One former BMS Senior Product Manager admitted that Baraclude was "somewhat slow to gain market share … [i]n comparison to what was expected." A53-54 (quoting A1319 (1258:21-1259:3)).

It was not until three years after its launch that Baraclude finally caught up with the market leader, Hepsera (adefovir). A53. And even then, Baraclude did not lead the market for long. After Viread (tenofovir) entered in 2008, Baraclude's market share stopped gaining momentum. A1325. Within 10 months, Viread

gained 28% of the market—a level that Baraclude only reached, with less competition, after 30 months. A54. By 2010, Viread had caught up to Baraclude and BMS had to stop using "#1 Prescribed" materials. *Id.*

6. Even though Teva copied entecavir, the district court found this evidence to be minimally persuasive due to the incentive created by the Hatch-Waxman act to copy FDA-approved drugs. A133-134 & n.39.

F. The district court's opinion

Based upon a careful analysis of the evidence and the factual findings summarized above, in a 171-page opinion devoted principally to this issue, the district court held claim 8 of the '244 patent invalid as obvious. *See* A1-73; A85-153. "[A]s to almost every significant portion of the *prima facie* case," the court concluded, "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." A152.

As for the objective considerations, the district court found the evidence "mixed" (A153) and ultimately overwhelmed by Teva's *prima facie* case: "Taken together, particularly in light of the significant force of Teva's *prima facie* case, and the fact that the PTO was not able to consider certain material prior art references regarding 2'-CDG during prosecution of the patent, the Court finds that Teva has demonstrated by clear and convincing evidence that claim 8 of the '244 Patent is invalid as obvious under Section 103." *Id.* (internal citation omitted).

SUMMARY OF ARGUMENT

The judgment of invalidity should be affirmed. The district court correctly began its analysis with this Court's "two-part inquiry" for assessing the *prima facie* obviousness of compound claims, considering: (1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts"; and (2) "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012). Here, at each step, the key evidence was undisputed. *That* is what drove the analysis, not hindsight. And, contrary to BMS's position, objective indicia only confirm, and certainly do not defeat, the *prima facie* case.

A. BMS's lead argument proposes a revolution in obviousness law. According to BMS, "[entecavir's] *unexpected* properties, which are 'inseparable' from the claimed compound, demonstrate *as a matter of law* that a person of ordinary skill in the art would not have had a reasonable expectation of success in making the claimed invention." BMS Op. Br. ("Br.") 34 (second emphasis added). This is incorrect. An invention is obvious where the prior art would have supplied a person of ordinary skill in the art at the time with reason or motivation to obtain the claimed invention with a reasonable expectation of success. *E.g.*, 35 U.S.C.

§103; *Otsuka*, 678 F.3d at 1292. Later-discovered and unexpected properties, therefore, do not defeat obviousness "as a matter of law" when, as here, the prior art would, nonetheless, motivate the POSA to obtain the claimed invention with a reasonable expectation of success.

BMS's argument to the contrary jumbles together precedents and principles involving expectation of success, motivation to combine, and objective indicia of nonobviousness. One telling flaw is that BMS's proposed legal rule is impossible to square with the decisions of this Court holding an invention obvious *despite findings of unexpected results*.

Another is that BMS's principal supporting authority—*In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963)—dealt with a different issue, in a different posture. The problem with the PTO's rejection of the claimed compound in *Papesch* was that, while the compound was "structurally obvious" and easily could have been made, its properties were so unexpected that it was not clear that anyone would have bothered to do so. But that is not the case here, and *Papesch* does not support BMS's proposed *per se* rule. Indeed, this Court sitting *en banc* stated in no uncertain terms that "*Papesch* is irrelevant to the question of the requirements for a *prima facie* case." *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (*en banc*). Nor does BMS find support in any of its other cited authorities, most of which involve

motivation issues or objective indicia. In short, BMS is just wrong: unexpected results do not *per se* preclude an expectation of success.

B. The district court correctly concluded that entecavir is exactly the kind of obvious compound that "would occur in the ordinary course without real innovation." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007). To overcome the factual determinations from which this conclusion inexorably follows, BMS must establish clear error. But it cannot do so. Indeed, far from depending on hindsight, as BMS now contends, the district court's findings are firmly planted in the prior art, what actual scientists in the field were doing at the time, and the opinions of *both* parties' experts.

In particular, by the time the application for the '244 patent was filed in 1990, others had already invented a compound, 2'-CDG, that was known to have the same antiviral properties BMS claimed in its patent for entecavir. There was overwhelming evidence that a person of ordinary skill in the art would have considered 2'-CDG a promising "lead compound" and would have pursued a finite number of obvious modifications to obtain other antiviral compounds. One of those obvious modifications—adding a *single carbon atom* at the 5' position of 2'-CDG—would have resulted in entecavir. And, in light of entacavir's structural similarity to 2'-CDG and the fact that this very modification had been made suc-

cessfully to other nucleoside compounds, a person of ordinary skill in the art at the time would have reasonably expected entecavir to be a successful antiviral agent.

These undisputed facts were confirmed by contemporaneous evidence of what researchers were actually doing and saying at the time—*i.e.*, heralding 2'-CDG's promising antiviral activity, using 2'-CDG as a lead compound in their own research, making the same and similar modifications, and successfully achieving antiviral properties as a result. Adding a carbon atom to 2'-CDG was an obvious extension of what was already known in the art—not a "real innovation" beyond it. *KSR*, 550 U.S. at 402.

Moreover, the PTO was never told that 2'-CDG even existed, let alone its promising and useful properties. As the Supreme Court has explained, the judgment of the PTO "may lose significant force" if it "did not have all material facts before it." *Microsoft*, 131 S. Ct. at 2251. That is the case here, which makes Teva's burden "easier to sustain." *Id.*

Now on appeal, BMS attempts to substitute lawyer argument for the experts who did not support its case—advancing interpretations of articles that no expert put forward. It is to no avail. BMS's reading of the art is wrong, and the conclusory cry of "hindsight" cannot be used to escape the undisputed evidence that entecavir was merely an obvious modification of a known lead compound.

C. The *prima facie* case is only confirmed by the objective indicia. That real-world evidence shows that others had succeeded in making similar compounds with antiviral activity, including against HBV—and that no one was skeptical that entecavir could achieve the same. To be sure, there was an unmet need for treating HBV in 1990. But *three other nucleoside analogs* that solved this need were invented and brought to market before entecavir. Entecavir has not been a blockbuster drug that altered the landscape of HBV treatments, or even the most commercially successful HBV drug. Nor does entecavir possess any properties that were truly "unexpected"; rather, its beneficial properties differ only in degree from prior compounds. Its potency, efficacy, and safety are good, but nothing unexpected for a nucleoside analog in light of the prior art.

In the end, far from defeating obviousness, this evidence confirms it. By 1990, the knowledge of nucleoside analogs had advanced to the point that researchers knew what was reasonably likely to produce an effective antiviral compound. That is why three other HBV treatments (all nucleoside analogs) were created before entecavir, and why no one was skeptical that entecavir, too, would work. Entecavir—like its FDA-approved competitors—is safe and effective. It was not, however, inventive. The judgment of invalidity should be affirmed.

ARGUMENT

I. Any Later Discovered, Unexpected Properties Of Entecavir Do Not Defeat The District Court's Reasonable-Expectation-Of-Success Finding "As A Matter Of Law."

As its lead argument, BMS contends that as a "matter of law" one cannot establish a reasonable expectation of success, and therefore obviousness, where there is evidence of unexpected properties. Br. 34-35. BMS's position misstates and would dramatically alter the law of obviousness. It should be rejected. The district court properly performed the reasonable-expectation analysis and properly considered BMS's evidence of later-discovered and (supposedly) unexpected results.

A. The reasonable-expectation-of-success analysis must focus on the prior art as it existed at the time of the invention.

When considering a POSA's expectations, the district court correctly considered the prior art as it existed at the time of the invention. It is fundamental that a patent may not be obtained if the claimed invention "would have been obvious *at the time the invention was made* to a person having ordinary skill in the art." 35 U.S.C. §103 (emphasis added). Accordingly, this Court has stated repeatedly that art published after the priority date is *irrelevant* to the expectation-of-success analysis; "[o]bviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art at the time of the invention." *E.g.*, *Velander v. Garner*, 348 F.3d 1359, 1377 (Fed. Cir. 2003) (citation omitted).

As for unexpected properties discovered after the time of the invention, BMS's own authorities show that these are considered as part of the larger obviousness inquiry—specifically as objective indicia of obviousness. *See Knoll Pharm. Co. v. Teva Pharm., USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (cited at Br. 36); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307-08 (Fed. Cir. 2011) (cited at Br. 37). But unexpected properties not known at the time of the invention do not defeat as a matter of law the reasonable expectation of success where, as here, other properties *that were reasonably expected* would have motivated a POSA to obtain the claimed invention regardless.

BMS's contrary position is inconsistent with numerous decisions of this Court finding a reasonable expectation of success *despite the presence of unexpected results*. *See, e.g.*, *Allergan, Inc. v. Sandoz Inc*., __ F.3d __, 2013 WL 1810852, at *6 (Fed. Cir. May 1, 2013); *Alcon Research, Ltd. v. Apotex Inc*., 687 F.3d 1362, 1365, 1369-70 (Fed. Cir. 2012); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

BMS attempts to distinguish *Pfizer* by highlighting the holding that the patentee had "simply failed to prove that the results are unexpected." Br. 35 n.6 (quoting 480 F.3d at 1371). But the Court's analysis did not stop there:

> Alternatively, *we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case*. Although secondary considerations must be taken into account,

> *they do not necessarily control the obviousness conclusion*. Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient.

Pfizer, 480 F.3d at 1372 (emphasis added) (internal citation omitted). Unexpected results must be taken into account as objective indicia, as they were here—but they do *not* "necessarily control the obviousness conclusion," *id.*, as BMS contends.

Take *Allergan*, for example. The claimed invention involved a combination therapy that unexpectedly solved an "afternoon trough" problem with separate dosages. This Court recognized this unexpected result (as an objective indicia)—and yet held the formulation claims obvious nonetheless. *See* 2013 WL 1810852, at *6. The reason? The POSA would have been motivated to pursue the claimed formulations to "achieve better patient compliance." *Id.* Given that reasonably expected, readily achievable benefit, the obviousness analysis did not turn on the fact that there were also unexpected benefits. *See id.* ("Whether or not that combination also solved problems associated with the afternoon trough, we find the motivation to make the combination was real.").

BMS attempts to distinguish *Allergan* on the ground that it involved both formulation and method claims (Br. 62 n.10), but the Court expressly found that the POSA would have been motivated by reasonable expectations of increased patient compliance to create the new formulations—and held the unexpected results irrelevant to that determination. That the Court did not reach the same result with

respect to the method claims (which involved additional *dosing* limitations) does not change that principle, but only reflects the *fact* that increased patient compliance provided a motivation and reasonable expectation of success for the formulation, and not the method. *See Allergan*, 2013 WL 1810852, at *6.

Likewise in *Alcon*, the Court held it obvious to use a compound in a particular, claimed concentration despite affirming a finding of unexpected results. *See* 687 F.3d at 1365, 1369-70. Again, the reason the claims were rendered obvious was the existence of a disclosure that would have motivated use of the compound in the claimed concentration for a different purpose, with a reasonable expectation of success. *See id.* at 1369 ("The district court's fact finding that the prior art did not teach that olopatadine would stabilize human conjunctival mast cells, and indeed taught away from using olopatadine for this purpose, is not clearly erroneous. It is, however, not the only motivation to arrive at the claimed invention…."). The Court also made clear that the reasonable expectation of success need only go as far as the basis disclosed in the patent. *Id.* (finding a reasonable expectation of success because "[t]he patent is not based on testing in humans; instead it reports only *in vitro* tests.").

Thus, BMS is simply wrong in its contention that "the court's recognition that entecavir possesses several unexpected therapeutic properties *alone* demonstrates that a skilled artisan would not have had a reasonable expectation of success

in creating the claimed invention." Br. 29 (emphasis altered). The patent claims the compound itself, *not* any particular therapeutic use—and the POSA would have sought (and expected to obtain) that compound based on the reasonable expectation that entecavir would have good antiviral activity. *See* A45-47, A102-108, A127-130 (detailing basis for reasonable expectation of success, including 2'-CDG's known properties and close structural similarity to entecavir); *infra* at 37-43 (selection of 2'-CDG as lead compound), 43-53 (addition of a double-bonded carbon to the 5' position), 56-57 ("unexpected" results).

In short, as the *en banc* Court explained in *Dillon*, 919 F.2d at 697:

> Properties … *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound, but it is not required … that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a *prima facie* case of obviousness.

B. BMS mistakes the import of post-invention discoveries, which do not preclude obviousness as a matter of law.

To support its proposal for a new rule that later-discovered and "unexpected" properties preclude a reasonable expectation of success as a matter of law, BMS points to cases that hold that "'a compound and all of its properties are inseparable' for purposes of evaluating obviousness." *E.g.*, Br. 33 (quoting *Papesch*, 315 F.2d at 391). This is a fatally incomplete statement of the law. As discussed above, for purposes of the reasonable-expectation inquiry, it is the evidence that

the POSA would have had *at the time* of the invention that is relevant. Unexpected properties of the compound that became known only after the invention date do not prevent a finding of reasonable expectation, but are considered as objective indicia and as part of the overall determination of obviousness. This is precisely what the district court did. *See infra* at 55-59.

There is in fact no case, either cited by BMS or to our knowledge, that articulates BMS's principle that unexpected results render a POSA's reasonable expectations impossible as a matter of law. BMS cases do not. As noted above, *Genetics Institute* and *Knoll* (cited at Br. 36-37) discuss post-invention evidence solely with respect to objective indicia—not with respect to a reasonable expectations analysis—and do not state that such evidence precludes a finding of reasonable expectations as a matter of law.

Nor can this be found in *Papesch*, an old decision by this Court's predecessor on which BMS relies heavily. *See* Br. 3, 29, 33, 34, 36, 37, 62 n.10. In that case, the Patent Office rejected a compound claim as obvious solely because of the compound's structural similarity to a prior art compound, and without regard for either compound's properties. This was despite test results showing that the claimed invention was an anti-inflammatory agent, while the prior art compound was not. *See* 315 F.2d at 382-83. The Patent Office reasoned that the applicant had sought to patent the *compound*, as opposed to its *use* as an antiviral agent—and

the compound itself was "structurally obvious." *Id.* at 383-84. On appeal, the Court of Custom and Patent Appeals reversed, faulting the Patent Office for its "failure to take into consideration the biological or pharmaceutical property of the compounds" in any respect. *Id.* at 391.

Significantly, in evaluating that error, the court relied on and reaffirmed precedent reasoning that "[t]he mere fact that it is possible to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious *unless the art also contains something to suggest the desirability of the proposed combination*." *Id.* at 389 (citation omitted) (emphasis added). This standard supports the district court's analysis here: quite apart from any later-discovered properties of entecavir, the prior art did indeed "suggest the desirability" of producing entecavir. *See* A112-127.

What is more, the *Papesch* court took the opportunity to reaffirm that unexpected properties do *not* guarantee that a new compound is patentable, and that a "mere difference in degree" as to an expected property is not enough:

> Patentability is not resolved conclusively even where unexpected or unobvious beneficial properties are established to exist in novel members of a homologous series over prior art members, as the circumstances of the case may require a consideration of other factors. A mere difference in degree is not the marked superiority which ordinarily will remove the unpatentability of adjacent homologues of old substances.

315 F.2d at 392 (quoting *In re Henze*, 181 F.2d 196 (C.C.P.A. 1950)) (internal cita-

tion omitted). And if that were not clear enough, in *Dillon*—a case not cited by BMS—the *en banc* Court not only held *Papesch* "irrelevant to the question of the requirements for a *prima facie* case," it also confirmed that "the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter[] does not by itself defeat a *prima facie* case." 919 F.2d at 697, 693.

Nor are BMS's other authorities to the contrary. To the extent they involve the expectation-of-success prong at all, they do not suggest, much less hold, that a reasonable expectation of success cannot exist as a matter of law just because unexpected results also are present—particularly where, as here, the "unexpected" aspects of the invention were but a modest difference of degree over the prior art.[1]

[1] *See In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517-18 (Fed. Cir. 2012) (language quoted at Br. 33 comes from a sentence characterizing the party's argument, which was that "*the prior art* provided no suggestion of [the invention's] unexpectedly superior properties …"; and the Court's own analysis was that the prior art provided no motivation to modify) (emphasis added); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361-62 (Fed. Cir. 2007) (cited at Br. 33) (affirming finding that "there was no reasonable expectation that [the inventive compound] would possess the desirable property of nontoxicity, particularly in light of the toxicity of [the prior art lead compound]" known at the time); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (cited at Br. 33) (affirming ruling of nonobviousness on ground that the prior art provided no motivation to modify existing compounds to obtain the invention, where challenger showed only that the POSA would have expected a certain "baseline level of activity" on par with "tens of thousands of compounds," as opposed to "high activity, few side effects, and [non-]toxicity"); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (cited at Br. 34) (affirming ruling of nonobviousness because prior art taught away; stating that unexpected properties "may lead to nonobviousness," not that the such results preclude obviousness).

Finally, BMS argues that toxicity information about the prior art compound 2'CDG that became known only *after* the invention of entecavir prevents a finding of a reasonable expectation. But there is no question that at the time of the invention the comparative properties of 2'CDG were *not* known and therefore information such as later-discovered toxicity would not have influenced the POSA's expectations. *See* A30-33; A105-107; A1258-1259 (BMS expert Dr. Tennant). As this Court affirmed in *Velander*, "it would be wrong to impute later-recognized insights—or possible obstacles—to the knowledge available to those skilled in the art at the time of the invention." 348 F.3d at 1377 (citation omitted).[2]

BMS insists that, "[a]s a matter of law, a reasonable expectation of success cannot rest on incorrect assumptions about similarities between two compounds." Br. 37. To support this proposition, however, BMS relies entirely on a single line taken out of context from *Papesch*—"[a]n assumed similarity based on a compari-

[2] Even if it were proper to consider post-invention art (it is not), 2'-CDG's later-determined properties would not have been a deterrent. First, 2'-CDG's later-determined higher toxicity was an unexpected property of 2'-CDG, not of entecavir. And, in any event, as the district court recognized, the record shows that medicinal chemists modify lead compounds that are potent even if also known to be toxic. *See, e.g.*, A34 (finding that, "[e]ven if some evidence did exist prior to 1990 indicating that 2'-CDG was associated with toxicity, such evidence … would not have discouraged the ordinary medicinal chemist from using 2'-CDG as a lead compound"); A106 n.23 (Madhavan group "used aristeromycin as a lead compound—a carbocyclic analog known to have toxicity associated with it"). Second, the later-determined potencies of 2'-CDG and entecavir are the kinds of differences of degree that do not affect patentability (*supra* at 18-19, 32), and plainly did not deter actual use of 2'-CDG as a lead compound (*infra* at 40-43).

son of formulae must give way to evidence that the assumption is erroneous." *Id.* (quoting 315 F.2d at 391). As noted above, however, *Papesch* held that it was error to reject a compound claim as obvious solely based on structural similarity. *Dillon* confirmed that *Papesch* did *not* hold that post-invention unexpected results bar a finding of obviousness as a matter of law.[3]

In sum, the district court did not commit legal error in finding that the prior art would have given a POSA a reasonable expectation of success, despite what was later discovered about 2'-CDG's toxicity or entecavir's "unexpected" properties. The district court properly considered unexpected results as part of its objective indicia analysis and its consideration of the evidence as a whole.

[3] BMS also remarks that an assessment based on then-existing prior art—that is, the art before "the time the invention was made," 35 U.S.C. §103—"would oddly suggest that a reasonable expectation of success could exist in 1990 when 2'-CDG's toxicity was not well-established, but not a few years *later* when 2'-CDG's toxicity was conclusively proven." Br. 37. This is an ironic complaint, given BMS's contention that a later-discovered, unexpected property should *per se* defeat obviousness—which would "oddly" mean that the claimed invention was obvious from at least 1990 to 1994, but then became non-obvious sometime thereafter as entecavir's "unexpected" therapeutic properties became known. In any event, odd or not, Congress has spoken: knowledge of the later-discovered fact of 2'-CDG's toxicity may not be imputed to a POSA working at the time of the invention.

II. The District Court's Obviousness Findings Are Not Clearly Erroneous; They Follow Not From Hindsight, But From The Record Evidence—Including The Testimony Of BMS's Own Expert.

The district court correctly held that entecavir is exactly the kind of obvious compound that "would occur in the ordinary course," and thus does not merit the protection of a patent. *KSR*, 550 U.S. at 402. There is no clear error in that decision. It is well-supported by the prior art, evidence of what researchers were actually doing and saying at the time, and the testimony of *both* parties' experts.

For purposes of this appeal, BMS breaks down the invention path into six steps that, in aggregate, supposedly pose a "multitude of possibilities leading far away from entecavir." *See* Br. 30, 39-56. We do not agree that BMS's "steps" have accurately captured the POSA's decisionmaking process. BMS would have the process appear complicated, but it is not: the POSA would have selected 2'-CDG as a lead compound, and developed that compound by making changes as suggested by the prior art. But even taking each of BMS's decision points in turn, there is little question what choice the POSA would have made, or that those choices would have led directly to entecavir. BMS's allegations of "hindsight" are just a thinly veiled attempt to contest the district court's factual findings without having to show clear error—a showing impossible for BMS to make.

A. Carbocyclics were the clear choice over furanosides and acyclics.

The law does not require assessment and exclusion of *every* possible alternative lead compound. Rather, a challenger must present one or more leads that a POSA "would have had a reason to select from the panoply of known compounds," *Otsuka*, 678 F.3d at 1292, based upon its "promising useful properties," *Daiichi Sankyo Co. v. Matrix. Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). In fact, this Court has explicitly rejected the proposition that the prior art must point to one and only one lead compound. *See id.*; *Altana Pharm AG v. Teva Pharm. USA., Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

Here, there were three classes of nucleoside analogs known in the art: furanosides, acyclics, and carbocyclics. A18. The district court assessed all three, found a POSA would have focused on carbocyclics, and concluded that "one of ordinary skill in the art would have had a reason to select [2'-CDG] over other compounds in the prior art." A94 (citation omitted). BMS argues that the district court committed legal error by "failing to consider the other possible lead compounds." *i.e.*, the furanosides and acyclics. Br. 42-43. This, however, is simply inaccurate. The district court explained that the field for furanosides and acyclics was "crowded" and "fairly well developed" to the point that a POSA would have had a "hard time finding [a furanoside or acyclic that] someone else hadn't already

tried"—making it less likely that a new, better, and more active compound would be found from those classes. *See* A19-20, A94 (citations omitted).

In marked contrast, the field for carbocyclics was "fertile" with "growing interest" (A21 (citations omitted)), and many scientists were pursuing carbocyclics with excitement and success. *See* A96 ("good antiviral activity appeared to be the rule rather than the exception among carbocyclic nucleosides") (quoting A2130); A97 ("[b]y far the most active and selective agents" were carbocyclic nucleosides) (quoting A2138); A21-22 ("[t]here is considerable current interest in the synthesis of carbocyclic nucleosides in our laboratories and elsewhere") (quoting A4020). In fact, BMS's own expert testified that in his lab at the time, working with carbocyclics "was most of what we did." A20 (quoting A1303). And BMS itself was successfully synthesizing carbocyclics at the time—including lobucavir, which it touted in a prior art article as having "excellent" antiviral activity, superior to a well-known acyclic, acyclovir. A22 (quoting A1226). (Acyclovir is a compound that BMS concedes was "frequently used as the standard[] against which to measure the antiviral activity of newly developed compounds." Br. 11.)

In the teeth of this record, BMS argues that the POSA would have chosen a furanoside or acyclic instead. But the district court did exactly what must be done to avoid hindsight—focus on the art that existed at the time. What is more, the

critical points were not only conceded by BMS's own expert, Dr. Schneller; "in 1989, *BMS itself* was touting the promise exhibited by carbocyclics." A95.

First, BMS points out that the FDA had yet to approve a carbocyclic. Br. 40-41. But that would not have stopped a hypothetical POSA any more than it stopped medicinal chemists in the real world. Practitioners were "regularly synthesizing carbocyclics in the late 1980s and beginning of the 1990s"—and finding that carbocyclics had increased activity compared to furanosides and acyclics. A20-24. For example, 2'-CDG was known to have surpassed both acyclovir, and the most commonly known furanoside, Ara-A, both of which were FDA-approved. *See* A24; A27. The lack of FDA approval would not have given the POSA pause.

Second, BMS relies on the fact that entecavir's inventor, Dr. Zahler, selected an acyclic as a lead in *1986*. Br. 41; *see* A96. But this Court has "repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had." *Alcon*, 687 F.3d at 1368 (reversing finding of nonobviousness). Moreover, as the district court pointed out in rejecting this same argument, the critical date here is *1990* (not 1986)—and by 1989, Dr. Zahler had not only turned to carbocyclics; he had published prior art that would have encouraged a POSA to do the same. A96.

Third, BMS contends that "at least one reference … directly disparaged the antiviral activity of carbocyclics." Br. 41 (citing A2091). But no expert testified

that this article would have deterred a POSA from pursuing carbocyclics. This is just the opinion of BMS's attorneys—which carries no weight. *Outside the Box Innovations, LLC v. Travel Caddy, Inc.*, 695 F.3d 1285, 1297 (Fed. Cir. 2012) ("it is technological experience in the field of the invention that guides the determination of obviousness, not the rhetorical skill or nuanced advocacy of the lawyer").

Further, as the district court acknowledged, this article found that the carbocyclic compound under review—a modified version of 2'-CDG, in fact—was 30 times more active than the "standard" acyclovir. *See* A28-29; A2090-2091. Tellingly, BMS contradicts itself in a later section of its brief, citing this very same article to show that, at the time of the invention, "numerous carbocyclics had potent antiviral activity." Br. 44-45.

Nor does BMS find the mark with its assertion that "[t]he district court's singular focus on carbocyclics is no doubt attributable to the hindsight bias relied on by Teva's expert Dr. Heathcock." Br. 42 n.7. The district court had no such "singular focus," and it correctly rejected this very attack on Dr. Heathcock because the record shows that he *did* consider the full scope and content of the prior art. *See* A94-95 n.13; A1041; A1073-1074.

B. There was no dispute that 2'-CDG was and would have been selected as a lead compound.

As the above analysis should already suggest, a POSA would have gravitated not just to carbocyclics, but to 2'-CDG in particular—a compound known to

have the sort of "promising useful properties" that motivate "a chemist to make structurally similar compounds," *Daiichi*, 619 F.3d at 1354; and "a natural choice for further development efforts," *Altana*, 566 F.3d at 1008.

Indeed, 2'-CDG was being used successfully as a lead compound at the time (A107)—and for good reason. In a 1989 article summarizing the state of antiviral research, Dr. Montgomery reported that 2'-CDG (and its prodrug forms) were "[b]y far the most promising" against herpes, and even more potent than the lead acyclic, acyclovir. A27 (quoting A2148, A2150); *see also* A1049. Previously published studies by the Southern Research Institute had likewise shown 2'-CDG to have "excellent activity" and "high potency," making it "much better than the marketed drug of the day." *See* A24 (quoting A2072); A1045. Shealy's 1985 patent further described 2'-CDG as "markedly more effective" against herpes than the existing approved drug, and a 1989 Price study reported that 2'-CDG had truly excellent activity against HBV. *See* A24-25 (quoting A1046, A2084); A26 (citing A1048, A2086).

Even BMS's expert, Dr. Schneller, conceded not only that 2'-CDG was being used as a lead compound by those in the art, but also that it met the requirements for a lead compound. *See* A27-28; A107-112; A1282 ("I agree ['2'-CDG] would be on the list" of lead compounds); A1295 ("I don't completely disagree" with Dr. Heathcock "on whether 2'CDG is a lead compound"); A1296 ("apparent-

ly others" thought "about 2'CDG as a lead compound back in that time period"); A1296 ("Q. And you understand there were people in the art at the time in the eighties who said 2'CDG was a lead compound? A. There were people that did that, yes, sir."). Additionally, one of Dr. Schneller's own publications touted 2'-CDG's "significant antiviral activity." A29 (quoting A4064).

BMS's counsel now proposes that a POSA would not have chosen 2'-CDG because another carbocyclic discussed in one article (Montgomery) had better antiviral activity. Br. 44 (citing A2149). This attorney argument is unsupported and wrong. It neglects that the carbocyclic in question is a prodrug form of 2'-CDG (that is, a compound that converts back to the parent compound once *in vivo*), *and thus owes its activity to 2'-CDG*. *See* A2149 Tbl. 6. Further, the evidence at trial—by those who actually know and are qualified to discuss the prior art, *Outside the Box Innovations*, 695 F.3d at 1297—was that this article *applauds* 2'-CDG: It says that the "most likely [antiherpetic] compounds appear to be the 2'-deoxyguanosine analog (CDG, 32) and its prodrug forms." A27 (quoting A2148); *see also* A1048-1049.

BMS argues that the district court's lead compound analysis rested on hindsight because the court looked to the structural similarity of 2'-CDG and entecavir. Br. 43. But structural similarity is a factor that the court was required to examine in the obviousness inquiry. *Dillon*, 919 F.2d at 692 ("structural similarity between

claimed and prior art subject matter … where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness"). Moreover, as the district court clearly stated, this was not the only factor in the lead-compound analysis. A98. Rather, the court also looked to the fact that 2'-CDG was being used as a lead in the prior art at the time and, per *Daiichi*, 619 F.3d at 1354, its biological properties—specifically that 2'-CDG had "high potency," "excellent activity," was deemed more effective than Ara-A and acyclovir, and was reported to be non-toxic as of 1990. *See* A102-112.

In any event, BMS's own expert conceded that 2'-CDG would have been viewed as a potential lead compound, Teva's expert agreed, and, as detailed above, *this was in fact happening in the real world at the time*. *See* A97; A107-112. This is not a matter of just eking by under the clear error standard; the evidence on this point was overwhelming. A POSA would have viewed 2'-CDG as "a natural choice for further development efforts." *Altana*, 566 F.3d at 1008.

C. It was obvious to focus on the carbocyclic ring—and no one says otherwise except BMS's attorneys.

The next decision point flagged by BMS is whether the POSA would try modifying the carbocyclic ring or the guanine base. Br. 47. But there is no question—a POSA would have modified the carbocyclic ring. A37; A113-115.

All experts, including Dr. Schneller, testified that a researcher employing the "traditional" method of drug discovery would have started with the most obvious,

conservative substitutions to 2'-CDG's structure. A37 (citing A1051, A1291, A1303). Between modifying the guanine base or the carbocyclic ring of the compound, the most obvious change would have been to modify the carbocyclic ring. A37. Modification of the guanine base on acyclic compounds had demonstrated "a substantial loss of antiviral potency," resulting in compounds that "were at least ten times less active." A37 (quoting A1052). As Dr. Heathcock testified, this evidence would have informed the POSA that "you don't want to mess with the guanine." A1052. In marked contrast, the prior art indicated increased antiviral activity following a change to the carbocyclic ring. A28-29.

BMS presented no evidence to the contrary. Its attorneys now advance interpretations of three pieces of prior art that supposedly point to a different conclusion—but without the support of any expert testimony. *Cf.* A115 n.28; A130 n.36.

First, BMS says that the Harnden and Jarvest article points to modifying the guanine base because two compounds with base modifications showed good *in vitro* activity. Br. 48. While no expert supports BMS's interpretation, the authors of the article themselves state that the base-modified compounds may have had good activity *only because their bases converted back to guanine*. *See* A114 n.27; A2012. Further, as Dr. Heathcock testified and the district court found, the point of the article is that "all" acyclovir analogs synthesized with base modifications by

a number of other researchers "resulted in substantial loss of antiviral potency." A114 n.27 (citations omitted).

Second, BMS's reliance on Montgomery (Br. 48-49) fails for the same reasons: it depends entirely on attorney argument with no expert support, and the two base-modified compounds were actually prodrug forms of 2'-CDG. *See* A2148; A1299. Which is to say, any activity observed from these compounds is attributable to the parent compound, 2'-CDG, not the base modifications. *See* A1049.

Third, BMS fares no better with the assertion that Marquez "discourages modifications to the carbocyclic ring" as "generally ineffective." Br. 49. With no expert support, BMS's counsel simply takes these statements out of context—the context being a compound where the 4' hydroxymethyl group was completely removed. *See* A2130. The failure of that dramatic modification would not have deterred a POSA from making a much simpler modification to the carbocyclic ring—which, no doubt, is why BMS did not make this argument at trial.

D. A POSA would have modified 2'-CDG at the 2' or 5' positions.

The most conservative and obvious places to modify the carbocyclic ring would have been the 2' or 5' positions. A37 (citing A1051-1052). In these positions, small modifications could readily be made, while substitutions at other locations on the ring (like the Marquez modification just discussed) could cause the molecule to become unrecognizable by the cell's "biochemical machinery." *See*

A37-38 (citation omitted). Dr. Heathcock so testified without contradiction from Dr. Schneller. A115 & n.28. BMS does not dispute the point now.

Instead, BMS complains that only in hindsight would a POSA modify the 2' position instead of the 5' position. Br. 50-51. But BMS neglects the art and testimony pointing to the 5' position. *See* A41, A115 n.28. And, more to the point, the district court did not find that a POSA would have chosen the 5' position *instead of* the 2' position. Teva argued, and the district court agreed, that a POSA would have had a finite number of obvious choices involving a conservative modification at *either* 2' or 5'. *See* A115-117. As the district court stated, no expert refuted this testimony, and BMS's arguments to the contrary were not persuasive. A115 n.28. This factual finding is exceptionally well-supported.

E. It was undisputed that the most conservative modification to make involved carbon.

Both experts testified that, to determine what modification to make to the 2' or 5' position, a medicinal chemist would have looked to the periodic table—and, in particular, to the top row, which contains the elements that are smallest in size and make the shortest bonds. *See* A38 (citing A1303-1304 (Schneller); A1052 (Heathcock)). Seeking the smallest and most conservative modifications, the medicinal chemist would quickly rule out many of the elements in the top row as too toxic, too reactive, or not reactive at all. A38 (citing A1052-1053, A1304). Dr. Heathcock opined that the most obvious remaining choices were carbon and fluo-

rine. A38 (citing A1053). And Dr. Schneller narrowed the choices still further—testifying that the "only one that sticks out" for an obvious, conservative substitution is carbon. A38 (quoting A1304-1305).

Citing references that disclose modifications using other elements, BMS now contends that a POSA would not have focused on carbon or fluorine. Br. 51-52. But BMS's assessment of these references is, again, bereft of expert support. BMS also neglects that most of its cited references were not encouraging: they note that another element was used, but then either fail to report whether the resulting compounds had antiviral activity, or report that the compounds had reduced or no activity. *See* A2008 (noting that compound 1f was not a potent inhibitor of cancer cells); A2119 (reporting no activity data from which to draw a conclusion); A2144-2145 (finding that chlorine, bromine, and sulfur substituents "reduced both potency and efficacy") (compounds 11, 12, and 14).

Moreover, *both* experts testified that a POSA would have looked to the first row of the periodic table—and to carbon in particular. A38; A1052-1053; A1303-1306. The fact that researchers in the field attempted the use of other elements speaks past this testimony; it does not contradict the experts' agreement as to the *most obvious* choice.

F. The POSA would have added a methylene group.

To make a carbon modification, the obvious, more conservative choice would have been a methylene group (carbon attached by a double bond) over a methyl group (carbon attached by a single bond) because a methylene group is smaller, and would "increase[] the surface area and volume of the molecule the least." A39-40 (quoting A1053). A single-bonded methyl group, by contrast, would have added not only a carbon, but two hydrogen atoms to the overall structure. A39 (citing A1053, A1306).

Dr. Schneller conceded that substituting a methyl group would have been "a conservative change" (A39-40 (quoting A1306))—and substitution of a methylene group was more conservative still. This is in part because the easiest way to add a methyl group would have been to *first* make the double-bonded carbon (the methylene group) substitution. A40 (citing A1053). In other words, even if a POSA wanted to make a methyl substitution, her route to do so would have entailed making the methylene substitution anyway.

Additionally, the prior art pointed to substituting a methylene group to gain antiviral activity. *See* A40-41. Specifically, the Takenuki and Ueda references disclosed antiviral activity from the substitution of a methylene group at the 2' position. A40-41. And of all the compounds synthesized by the Madhavan group, the one produced by a methylene substitution at the 5' position was the most po-

tent. A41 (citing A2002-2003 (compound 30), A1055). BMS disclosed Madhavan to the PTO as the closest prior art. A168-169. And even BMS's expert ultimately admitted that Madhavan would have encouraged a POSA to modify the 5' position of 2'-CDG with a methylene group. A122-123 (discussing A1311-1312).

BMS's attack on this factual finding fails to show clear error. First, BMS contradicts its own expert and asserts that Madhavan would have discouraged this modification because the Madhavan compound was toxic. *See* Br. 53. As the district court determined, however, there was no evidence that this toxicity was due to the addition of the methylene group; the Madhavan compound was created from the lead compound aristeromycin, which was already known in the prior art to be cytotoxic. A42; A124 (quoting A1055). BMS flags other modifications discussed by Madhavan that produced less toxic compounds (Br. 53), but *all* of the Madhavan compounds created using aristeromycin showed toxicity (A2003, Tbl. 1), and the attempt by BMS's attorneys to attach significance to the relative toxicity of certain compounds is, yet again, unsupported by expert testimony.

BMS also neglects the Takenuki and Ueda references. They teach that adding methylene groups to the carbocyclic ring resulted in compounds with antiviral activity. *See* A40-41; A125.

Second, BMS argues for the first time that Dr. Schneller's concession that carbon is the "only" element that "sticks out" was only meant to pertain to a me-

thyl group. Br. 54. But that is not what Dr. Schneller said. *See* A1305; *see also* A117 & nn. 29-30 (evaluating Dr. Schneller's deposition and trial testimony).

Third, BMS also attempts to rewrite Dr. Schneller's testimony regarding Madhavan—arguing now that when Dr. Schneller conceded that Madhavan's toxicity "might not dissuade" a POSA from adding a methylene group, he "was merely opining that a person of ordinary skill in the art likely would not consider the Madhavan compounds at all." Br. 54 (citation omitted). When asked about this statement on cross-examination, however, Dr. Schneller himself made no such clarification:

> **Q.** All right. And, sir, you actually said under oath in your deposition that the Madhavan article *could have led* a person of skill in the art to seek drug discovery targets guided by combining the features reported in Madhavan with those in Shealy. You said that in your deposition, didn't you?
>
> **A. Yes, sir.**
>
> **Q.** That's very different from saying that Madhavan would discourage somebody from making that substitution.
>
> **A. Yes, sir.**
>
> **Q.** So, sir, when you testified under oath and you wrote your expert report and you signed it, you were giving us truthful, honest testimony about your opinions; is that right?
>
> **A. Of course.**
>
> **Q.** And we can count on those; is that right?
>
> **A. Yes, sir.**
>
> **Q.** We can rely on those as your true opinions in this case?

A. Yes, sir.

A1312 (emphasis added) (quoted at A123). Tellingly, BMS did not address this on redirect. And, again, making sense of this sort of shifting testimony is part of the district court's job as fact-finder. Even if BMS's newly raised, alternative interpretation were reasonable, it would not establish clear error in the district court's finding that these "powerful admissions by BMS's expert severely undercut BMS's arguments to the contrary regarding motivation to combine." A124. *See Delaware Valley Floral Group, Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1381 (Fed. Cir. 2010) ("Issues of credibility and the weight afforded certain evidence are determinations appropriately made by a finder of fact ….") (citation omitted).

Fourth, citing Dr. Heathcock's testimony, BMS asserts that "the addition of a methylene group was not the only carbon-based substitution that a person of ordinary skill in the art would have considered." Br. 55. But BMS ignores that it was undisputed that the easiest way for a POSA to make a methyl group substitution would be to *first* make a methylene substitution. A40; A117-118 n.30. Given that the methylene substitution would be made first, the district court reasonably found that this is the more conservative modification and one POSA would have tried. *See* A39-40; A126.

Finally, BMS argues that there was "no evidence offered at trial" that the size of a substitution was a determining factor. Br. 55-56. This is incorrect. Dr.

Heathcock testified that a POSA would have gravitated to a methylene substitution because it would not "increase[] the surface area and volume" of the molecule as much. A39 (quoting A1053). And both experts agreed that a POSA would have taken the traditional approach and made the smallest, most conservative changes to the lead compound. A37 (citing A1051, A1291). That points directly to a methylene group. *See* A39-40; A1053; A1306. Yet again, there is no clear error in the district court's factual finding.

G. The claimed compound was one of a finite number of obvious modifications.

As the district court found, ultimately there were six obvious solutions for a POSA to pursue: at each of the two positions, two ways to bind a fluorine atom and one way to bind a double-bonded carbon atom. A39 (citing A1053-1054; A4001). One of these had already been identified in the prior art (*see* A28-29; A117-118), leaving five obvious modifications for the POSA. Far from being a truly inventive leap forward, entecavir was one of just a handful of obvious, conservative modifications that a POSA following the traditional approach would have tried "in the ordinary course." *KSR*, 550 U.S. at 402.

Citing *Rosuvastatin*, 703 F.3d at 518, BMS points out that entecavir was not developed by others before BMS improperly fenced off the field in 1990. *See* Br. 57-58. But *Rosuvastatin* did not accept this argument, which would erase the obviousness doctrine altogether. Rather, obviousness was negated in that case by a

deep-seated skepticism in the field about the type of compound claimed, and the fact that practitioners had *abandoned* the pertinent structure. *See* 703 F.3d at 518. Here, there was no skepticism or abandonment but rather great enthusiasm surrounding carbocyclics and 2'-CDG. *See* A20-23; A26-30.

Finally, BMS contends that the solutions here were not predictable because small changes to nucleoside analogs may result in different biologic activity. *See* Br. 59. But "[o]bviousness does not require absolute predictability of success." *In re Droge*, 695 F.3d 1334, 1338 (Fed. Cir. 2012). Even in the chemical arts, where there is "some degree of unpredictability," advances are not *per se* patentable. *Pfizer*, 480 F.3d at 1364; *accord In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). And here a POSA would have reasonably expected that a conservative change to 2'-CDG would produce an effective, non-toxic antiviral.

In sum, the district court found that 2'-CDG would have been selected as a lead compound, and there would have been every expectation of success in obtaining the claimed invention—because of 2'-CDG's good antiviral activity, and because other practitioners in the art were adding methylene groups to compounds with success. This decision was based on a thorough analysis of the evidence and findings of fact well-supported by the prior art, actual experimental choices made by real researchers at the time, and the testimony of *both* experts.

III. The Objective Indicia Only Confirm Obviousness.

A. An invention may be obvious despite the existence of objective indicia of nonobviousness.

According to BMS, the ultimate conclusion of obviousness cannot be squared with the district court's findings on the objective considerations. Br. 61-62. But in fact, this Court has found objective evidence dispositive only "rarely." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1354 (Fed. Cir. 2012). Moreover, BMS's own cited authorities make clear that the mere existence of objective evidence of nonobviousness "may" establish that an invention appearing obvious was not. *E.g.*, *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-76 (Fed. Cir. 2012) (citation omitted). BMS says that even a single objective factor can support obviousness. Br. 64. But so what? Even where multiple indicia are present, a claimed invention is not necessarily non-obvious. *E.g.*, *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("substantial evidence of commercial success, praise, and long-felt need" was "inadequate to overcome a final conclusion that claim 25 would have been obvious").

Nor is it legal error to decide—upon reviewing the evidence as a whole, as the district court did here (A152-153)—that evidence of objective considerations is insufficient to "overcome" a *prima facie* case of obviousness. *See Novo Nordisk*

A/S v. Caraco Pharm. Labs., Ltd., __ F.3d __, 2013 WL 2991060, at *6 (Fed. Cir. June 18, 2013).

B. The objective indicia evidence was weak.

Much of the evidence BMS presented regarding its alleged objective considerations was "not … particularly compelling." A152. For example, the district court found that there was no failure of others or real skepticism surrounding entecavir. Rather, the evidence showed that others were succeeding in developing compounds with antiviral activity, including against HBV. A142-143 (the evidence "highlights that *numerous* drugs for the treatment of hepatitis B have been developed and approved by the FDA"). And the uncorroborated skepticism testimony of BMS's Dr. Gish was unpersuasive. A140. Similarly weak was BMS's assertion of copying, because a central purpose of the Hatch-Waxman Act is to incentivize generic copies of name-brand pharmaceuticals. A133-134.

While the district court found that Baraclude's raw sales figures show commercial success (A135), Baraclude was "a less dynamic" success than BMS represented (A138). Baraclude took much longer to gain market share than did its competitors, Hepsera and Viread; although it launched in 2005, it was not until 2009 that Baraclude was able to establish itself as the number-one HBV drug on the market—and it lost that position again within a year. A136-137. Tellingly, even BMS viewed Baraclude's performance as "sub optimal." A137.

As for long-felt unmet need—the evidence cut *against* BMS. To be sure, in 1990, there was a need for an effective drug to treat HBV. A147. Entecavir later solved this need, *but so too did three other nucleoside analogs* (lamivudine, adefovir, and tenofovir), each of which was actually invented before entecavir, and approved before Baraclude. *See* A147-148. The fact that entecavir is one of *four* drugs that helped solve a need is hardly persuasive evidence of nonobviousness.

With regard to unexpected results, the district court found that entecavir's activity against HBV and low toxicity "could have been predicted at the time of entecavir's invention." A149-150; *see also* A45-46; A127-130. These are the most important properties of entecavir, and the fact that they were reasonably expected based on the prior art undercuts BMS's case for unexpected results. Further, although the district court found unexpected entecavir's potency, high genetic barrier to resistance, and large therapeutic window (A150-151), the evidence shows that entecavir's potency and therapeutic window were predictable based on the known properties of 2'-CDG at the time. *See* A102 (2'-CDG had "high potency" against HSV-2); A103 (2'-CDG had "excellent activity" and a "very good" therapeutic window against HBV); A127 (2'-CDG and entecavir are structurally similar, and structurally similar compounds often have similar properties). And entecavir's genetic barrier to resistance could not have been unexpected in 1990 because it was not known until much later that resistance was a problem. *See* A61;

In re Geisler, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) (alleged unexpected results must be judged against what "would have [been]] found surprising or unexpected" "at the time of [the] application").[4]

Despite these weaknesses, BMS now announces that objective indicia "overwhelmingly" show that Teva failed to carry its burden and that "unexpected results alone … can negate any affirmative evidence of obviousness." Br. 61-62. As explained above, however, a finding of unexpected results does not automatically preclude a finding of obviousness. *Supra* at 27-29 (discussing *Allergan*, *Alcon*, and *Pfizer*). And looking at the totality of the evidence, the district court correctly determined that BMS's weak showing on the objective indicia was overwhelmed by Teva's clear and convincing *prima facie* case. A153.

C. The district court made no legal error.

Finally, BMS casts about for legal error, but there is none.

First, BMS asserts that the district court committed legal error because it "discounted evidence" of unexpected results due to its comparison of entecavir to tenofovir, rather than to the closest prior art. Br. 62-63. But BMS itself compared entecavir to tenofovir in its unexpected results analysis! A8091-8092. Invited error is not a basis for reversal. *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 715 (Fed. Cir. 1998). Nor, in any event, is there error: The district court explicitly

[4] For this same reason, entecavir's non-toxicity is not an unexpected result. The surprise, rather, was that 2'-CDG was toxic.

recognized that "the results must be shown to be unexpected compared to the closest prior art." A148 (citations omitted). It merely noted in passing that certain properties of entecavir have not been found superior to tenofovir (*see* A151-152)—again, doing so in response to an argument that BMS itself had made.

Second, BMS contends that the district court discounted the evidence of unexpected results due to its reliance on the inventor's own expectations. Br. 63. But all agree—and the district court expressly recognized—that the inventors' expectations *as such* are not pertinent. A87. The district court used inventor testimony solely to "illuminate[] the properties that *a person of skill in the art* would have expected entecavir to demonstrate" *from the prior art*. *See* A150 (emphasis added) (citing *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 418 (S.D.N.Y. 2012)); *W.R. Grace & Co.-Conn. v. Intercat, Inc.*, 7 F. Supp. 2d 425, 463-64 (D. Del. 1997), *aff'd*, 155 F.3d 572 (Fed. Cir. 1998). Further, in correctly concluding that entecavir's improvement over existing compounds was only a matter of degree, the district court found independent support in "examples in the prior art, at the time of the invention, of compounds that also showed effectiveness against hepatitis B without known toxicity issues, including 2'-CDG." A150; *see also* A103; A2086.

Third, arguing that the district court weighed the various objective indicia of nonobviousness against each other, BMS compares the district court's analysis to

that in *Cylclobenzaprine*, 676 F.3d at 1080, where the lower court "focused on objective evidence that supported its obviousness determination, but ignored other evidence that cast the objective considerations in a light favorable to [the patentee]." Br. 64. But the district court here did not ignore anything. It discussed these considerations at length and, both within and across factors, the court agreed with BMS in some respects, Teva in others—which is to say, the district court exercised its own independent, considered judgment. *See* A131-152. BMS objects to the court's conclusion that these factors are "mixed" (A152), but there is no error in stating the reality that BMS supported some of its arguments and not others. And the fact is, several factors *do* reinforce Teva's *prima facie* case—in particular, the lack of skepticism and the fact that entecavir was the *fourth* nucleoside analog identified in this period that has proven successful for treating HBV.

At the end of the day, the best argument for affirmance is the district court's opinion. The court took into consideration all of the evidence presented, including evidence regarding the objective indicia, and—"particularly in light of the significant force of Teva's *prima facie* case and the fact that the PTO was not able to consider certain material prior art references regarding 2'-CDG during prosecution of the patent"—correctly held claim 8 invalid as obvious. A153.

CONCLUSION

The judgment of invalidity should be affirmed.

Dated: July 18, 2013

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on July 18, 2013, I caused the foregoing Brief of Defendant-Appellee Teva Pharmaceuticals USA, Inc. to be electronically filed with the Clerk of Court using the CM/ECF system, and thereby served via CM/ECF on the counsel for Plaintiff-Appellant Bristol-Myers Squibb Company.

Dated: July 18, 2013

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