

Bristol-Myers Squibb Co. v. Teva Pharmaceuticals: Exploring the effect of post-invention evidence of unexpected results on § 103 obviousness[†]

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I. INTRODUCTION

Entecavir is the active ingredient in Baraclude[®], which is approved for use in the treatment for hepatitis B. Baraclude[®] is a top-selling drug for Bristol-Myers Squibb (“BMS”), reaching \$240 million in U.S. sales and \$1.5 billion in worldwide sales in 2013 alone. Teva sought FDA approval to commercialize its generic version of entecavir, and the ensuing litigation resulted in a determination by a U.S. District Court that the BMS patent claim covering the entecavir compound was invalid as obvious under Section 103.

On appeal, in *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals*,¹ the Court of Appeals for the Federal Circuit affirmed the decision that BMS’ patent claim directed to entecavir was obvious in view of a prior art compound, 2’-CDG.² Seeking rehearing *en banc*, BMS argued that the panel opinion did not properly consider the post-invention evidence that 2’-CDG was toxic to mammals, thus defeating any reasonable expectation of success that a person of ordinary skill in the art (“POSA”) could have in starting with 2’-CDG as a lead compound. BMS also argued that the panel opinion incorrectly distinguished between “differences in degree” and “differences in kind” of unexpected results. *Amicus* briefs from many in the U.S. pharmaceutical and biological research industries likewise expressed concern that the panel decision rewrote the test for obviousness for pharmaceutical patents. The federal circuit denied the petition for rehearing in a *per curiam* decision, which at first glance appears to present fundamentally different views on whether post-invention evidence can be used to establish unexpected results.³

As discussed below, the federal circuit panel opinion did not depart from precedent or create new law limiting the use of post-invention evidence in a § 103 obviousness inquiry. Rather, as concluded by Judge O’Malley in her concurring opinion, the panel opinion merely affirmed a “fact dependent opinion” and “ma[de] no dramatic changes to the law.” The district court’s decision to excise from its analysis any consideration of 2’-CDG’s later-discovered toxicity accords with U.S. case law on obviousness and does not signal a new approach to litigating pharmaceutical patents.

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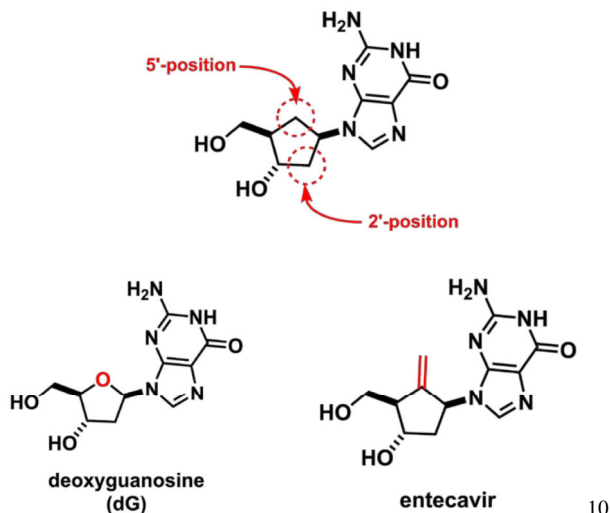
II. BACKGROUND

U.S. courts follow a two-part analysis in determining whether at the time of invention a claimed chemical compound would have been *prima facie* obvious over prior art compounds.⁴ First, a court determines whether a person of ordinary skill in the art (“POSA”) would have selected a particular prior art compound as a “lead compound” for further development efforts.⁵ A court then determines whether the prior art provided a POSA with motivation to modify the lead compound to make the claimed compound with a reasonable expectation of success.⁶ This expectation may be based upon a sufficiently close structural relationship between the lead compound and the claimed compound.⁷

A court must also consider objective evidence of nonobviousness, such as commercial success, long felt but unsolved needs, failure of others, unexpected properties, etc.⁸ “To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.”⁹ The *Bristol-Myers* opinions from the District of Delaware and the Federal Circuit revisit the contours of post-invention evidence of unexpected properties and its impact on the obviousness inquiry.

III. BRISTOL-MYERS SQUIBB CO. v. TEVA PHARMS.

BMS’s U.S. Patent No. 5,206,244 discloses and claims a genus of chemical compounds known as nucleoside analogs. The ’244 patent issued April 27, 1993, based on a priority date of October 18, 1990. The ’244 patent states that carbocyclic nucleoside analogs, like entecavir, differ from natural nucleoside deoxyguanosine by the replacement of an oxygen atom with an exocyclic methylene group at the 5’ position:



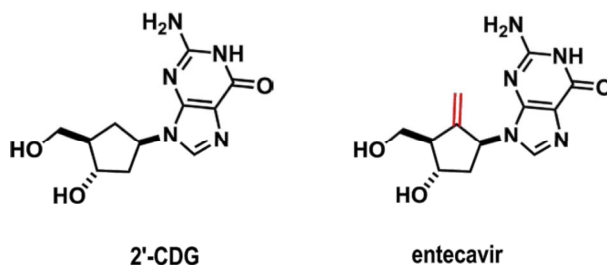
Deoxynucleosides are the building blocks from which DNA is made, and analogs like entecavir are used as antiviral drugs that interfere with the process by which a virus

reproduces itself through replication of DNA.¹¹ As depicted above, deoxynucleosides have a double ring “nucleoside base” and a five-membered ring “carbocyclic ring.”

Claim 8 of the '244 patent is directed to the chemical compound entecavir, which is an analog of the natural nucleoside deoxyguanosine.

a. District Court litigation

Teva filed an Abbreviated New Drug Application with a paragraph IV certification that claim 8 of the '244 patent was invalid and unenforceable, and BMS sued, claiming that the ANDA filing and the subject drug product infringed claim 8 of the '244 patent. Teva argued that claim 8 of the '244 patent was obvious under 35 U.S.C. § 103(a) based on the selection of certain lead compounds and the motivation to modify those compounds to obtain entecavir. Teva argued that a POSA seeking to make an antiviral compound in 1990 would have selected 2'-CDG as a lead compound and modified it to include an exocyclic methylene group at the 5' position to improve antiviral activity, as both were known. Entecavir differs from 2'-CDG only in the presence of an exocyclic methylene group at the 5' position, depicted in red:



The synthesis and activity of 2'-CDG was first published in 1984 by Dr. Shealy, who disclosed that 2'-CDG had greater *in vitro* antiviral activity against HPV than the best-selling drug at the time. Additionally, the district court observed that prior to 1990 others had also published articles on 2'-CDG's excellent activity against the herpes virus.

In 1988, G.V. Bindu Madhavan published antiviral studies on a nucleoside analog called “Madhavan 30,” which has an exocyclic methylene group at the 5' position on the carbocyclic ring in place of an oxygen atom. The Madhavan reference disclosed that substitution of the oxygen group with a methylene group led to significantly superior antiviral activities.

i. Selecting 2'-CDG as a lead compound

To select 2'-CDG as a lead compound, the court first observed that a POSA would have selected a lead compound from one of three classes of nucleoside analogs: acyclic, furanose, and carbocyclic nucleosides. Both parties' experts agreed that in the late 1980's, researchers were increasingly interested in carbocyclic nucleosides, while acyclic and furanose nucleosides had been quite actively investigated. The court thus found that a POSA would have selected a carbocyclic nucleoside as a lead compound.

The court next relied upon the parties' agreement that 2'-CDG and entecavir shared structural similarities. The court gave significant weight to a 1987 BMS article that referred to 2'-CDG as being "structurally similar" to entecavir. The article was written by a group of BMS scientists, including Dr. Zahler, a coinventor of the '244 patent. The court found that "[t]he fact that BMS and Dr. Zahler, well before this case began, were emphasizing the structural similarities between 2'-CDG and entecavir (and not noting any differences between them) is persuasive evidence to the Court that those similarities are compelling." Moreover, the court found that BMS used 2'-CDG in a computer modeling program to develop entecavir, based on the similar three-dimensional shape of the compounds. The court considered this "powerful corroborating evidence" of the structural similarities between the compounds.

In addition to the structural similarity between 2'-CDG and entecavir, the court cited articles published in the late 1980's as demonstrating that 2'-CDG was considered to have very good antiviral activity. BMS did not contest the disclosure of 2'-CDG in the literature, but rather argued that a POSA would not have selected 2'-CDG as a lead compound due to its toxicity. The court disagreed: "The significant problem with BMS's argument is that, as of October 1990, 2'-CDG was *not yet known* to have a high toxicity." The court further noted that BMS's expert witness, Dr. Tennen, testified that he was "absolutely not aware" of any toxicity associated with 2'-CDG, until he conducted his own experiments with the drug in 1990-1991. The court concluded that 2'-CDG's later discovered toxicity "would not have deterred the skilled chemist from selecting 2'-CDG as a lead compound during the relevant time period because *it did not exist* at the time, and thus could not have been available to that chemist."

Furthermore, the court emphasized that both parties' experts agreed that in the years leading up to 1990, medicinal chemists "were *actually treating and using* 2'-CDG as a lead compound during the relevant time period." The Court thus held that as of October 1990, the priority date of the '244 patent, a POSA would have selected 2'-CDG as a lead compound.

ii. Modification of 2'-CDG to produce entecavir

The court then found that a POSA would have had a reason or motivation to modify 2'-CDG to make entecavir. Teva's expert witness, Dr. Heathcock, testified that by the late 1980s chemists in the field had made modifications to the carbocyclic ring portion of nucleosides to yield compounds with increased activities. On the other hand, changes to the guanine base of nucleoside analogs resulted in decreased activity. Teva's expert further testified that because of 2'-CDG's structural configuration, a POSA would have focused on the 2' and 5' positions for modifying 2'-CDG. BMS's expert witnesses did not refute this contention.

Following testimony from both parties' experts, the court concluded that a POSA would have been motivated to make small, conservative changes to the 2' or 5' positions of 2'-CDG's carbocyclic ring to improve antiviral activity. In this regard, both parties' experts agreed that they would look to the top row of the periodic table for small potential replacements for the -H on the furanose portion of 2'-CDG. Teva's expert identified

carbon and fluorine as obvious choices for modification, and BMS's expert testified that he would "rule out everything but carbon." BMS's expert also agreed that in the 1980s, other chemists were adding an exocyclic methylene group to prepare nucleoside analogs, such as Madhavan 30. Based on the prior art and expert testimony, the court concluded that it would have been obvious for a POSA to add an exocyclic methylene group to the 5' position of 2'-CDG to produce entecavir.

iii. Secondary considerations of non-obviousness

Having found that Teva established a *prima facie* case of obviousness, the court turned to BMS's evidence regarding objective indicia of nonobviousness. The court found that Teva's decision to copy entecavir was not probative of nonobviousness in view of the incentive provided by the Hatch-Waxman Act. Baraclude® was found to be a commercial success, but less of one than BMS had asserted. The court also found BMS's uncorroborated testimony relating to skepticism of those in the art unpersuasive and similarly found evidence of failure of others to be weak. The court did find that a long felt need existed for a drug that could be effective against hepatitis B at the time that entecavir was developed, but that at least three other drugs were commercialized before entecavir met this need. Lastly, the Court noted that some of entecavir's attributes were unexpected and support of nonobviousness, such as entecavir's potency against HBV, its high genetic barrier to resistance, and the size of its therapeutic window. However, the Court ultimately held that the evidence of secondary considerations was insufficient to overcome Teva's strong *prima facie* showing of obviousness of claim 8. In a detailed 171-page opinion, the district court ruled that claim 8 was obvious, and therefore invalid.

b. Appeal at the Court of Appeals for the Federal Circuit

On appeal, a panel of federal circuit members affirmed the district court's holding that claim 8 was invalid under 35 U.S.C. § 103(a). The panel held that "the district court properly found strong evidence of obviousness, because the record shows that a skilled artisan would have selected 2'-CDG as a lead compound and made the minor modification to arrive at entecavir." The panel also found no clear error in the district court's fact findings regarding evidence of secondary considerations of nonobviousness.

Regarding the selection of 2'-CDG as a lead compound, the panel agreed with the district court that the evidence showed that carbocyclic analogs were attractive candidates for antiviral drug discovery and that 2'-CDG was a natural choice as "medicinal chemists during the relevant time frame *were actually treating and using* 2'-CDG as a lead compound." 2'-CDG's later-discovered toxicity did not change the panel's opinion in this regard. Rather, the panel agreed with the district court that at the time of the invention 2'-CDG was generally understood to be safe and nontoxic and thus a natural choice. In support of this position, the panel quoted *Velandier v. Garner*: "Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art *at the time of invention*."¹²

The federal circuit panel also found no clear error with the district court's holding that a POSA would have been motivated to modify the carbocyclic ring of 2'-CDG to

arrive at entecavir and would have had a reasonable expectation of success in doing so. Upon selecting 2'-CDG as a lead compound, the steps of deciding which position to modify and which modifications to make constituted a small, finite number of changes required to arrive at the lead compound. The panel thus concluded that BMS failed to establish clear error in the district court's factual determinations, which were based on the prior art and expert testimony.

BMS's evidence of objective criteria did not overcome Teva's strong *prima facie* case. On appeal, BMS focused its secondary considerations arguments on unexpected results. Citing *In re Dillon*,¹³ the panel explained that unexpected results do not *per se* render a compound nonobvious. Rather, "the expected properties of a claimed compound may be sufficient to lead to a reasonable expectation of success in modifying a prior art compound to make that claimed compound." The panel further distinguished differences in degree versus differences in kind, observing that differences in degree of a known and expected property are not as persuasive in rebutting obviousness as differences in kind. However, "a marked superiority in an expected property may be enough in some circumstances to render a compound patentable."

In considering BMS's unexpected results the panel found that entecavir's potency and good therapeutic window were not unexpected, since it was known that 2'-CDG was effective against hepatitis B and had a good therapeutic window. On the other hand, in line with the district court's findings, the panel found that entecavir's high genetic barrier to resistance was unexpected. However, this evidence was insufficient to overcome Teva's strong *prima facie* case.

c. Petition for rehearing at the Federal Circuit

Following the panel decision, BMS sought rehearing and rehearing *en banc* of the panel decision. BMS urged that the panel decision erred in (1) its treatment of post-invention evidence regarding the differences between the prior art and the invention; (2) its statement of what constitutes an unexpected result in the pharmaceutical context; (3) its consideration of which party carries the burden of proof in an obviousness inquiry; and (4) the weight given to evidence of objective indicia of nonobviousness.

On October 20, 2014, the federal circuit denied BMS' petition in a *per curiam* decision with Judges Dyk, Wallach, and O'Malley authoring concurring opinions. Judges Newman, Lourie, Reyna and Taranto wrote in dissent.

At first glance, the court members appear to present fundamentally different views on whether post-invention evidence can be used to establish unexpected results. For example, Judge Dyk's concurrence with the denial of rehearing *en banc* makes clear that "the pertinent knowledge is that possessed at the time of invention," citing *KSR*,¹⁴ and that the panel decision "properly [did] not allow consideration of post-invention evidence in the circumstances of this case."

Also concurring with the denial of rehearing *en banc*, Judge O'Malley acknowledged that federal circuit precedent "clearly allows the consideration of later

discovered differences between the prior art and the invention,” but that those differences “inform the obviousness analysis and thus can be considered when assessing what was understood by one of skill in the art at the time of the invention and what expectations may have been reasonable.” Thus, both judges agree that the focus must be on the understanding of those skilled in the art at the time of the invention, but Judge O’Malley explains that post-invention evidence could inform that inquiry. Here, Judge O’Malley viewed the district court and the panel as having considered post-invention evidence of differences, but not having found it sufficient to overcome the strong *prima facie* evidence of obviousness.

Dissenting, Judge Newman outlined four areas she believed the panel opinion departed from well-settled precedent.

First, she cited the failure of the court to properly weigh the evidence of the toxicity of 2’-CDG in comparison to entecavir. Certainly the district court and the panel opinions *did* consider the toxicity of 2’-CDG in analyzing secondary considerations, and so there is an apparent disconnect between the panel opinion, explained by Judge O’Malley in her concurrence, and the criticisms leveled against it by Judge Newman. Both the district court and the federal circuit panel stated that post-filing evidence of 2’-CDG’s toxicity did not affect the choice of 2’-CDG as a lead compound because it was not known to person skilled in the art at the time of filing. Rather, the Price reference and other prior art showed the toxicity of 2’-CDG to be well above its efficacy levels. As a result, a reasonable expectation of success was based on the knowledge to a POSA in 1990 that 2’-CDG was *not* toxic.

Second, Judge Newman criticized the federal circuit panel’s misapplication of secondary considerations based on her view that the panel arbitrarily placed a new restriction on the reliance on such information, stating that objective evidence of nonobviousness often does not come into existence until after the patent application is filed. But as the federal circuit panel discussed, BMS relied on post-filing evidence of entecavir’s high potency, large therapeutic window, and high genetic barrier to resistance as unexpected properties -- it did not specifically rely upon differences in toxicity between entecavir and 2’-CDG. The difference is important because while post-filing evidence could inform the secondary considerations analysis, it could not have informed the selection of the lead compound by a POSA. The district court and federal circuit panel analyses did not depart from precedent in explaining that the later-discovered toxicity of 2’-CDG compound would not dissuade its use as a lead compound when it was not known at the time of filing.

Third, Judge Newman disagreed with the court’s “holding” that an unexpected property is *per se* insufficient to show nonobviousness. But the panel opinion did not so hold. Rather, the panel relied upon the federal circuit *en banc* decision in *In re Dillon*¹⁵ for the proposition that “an unexpected result or property does not by itself support a finding of nonobviousness.”¹⁶ The federal circuit panel emphasized that in *Dillon*, the *en banc* court held that the expected properties of a claimed compound *may* be sufficient to lead to a reasonable expectation of success in modifying a prior art compound.¹⁷

Finally, Judge Newman disagreed with the panel's "oversimplified" distinction between differences in degree and differences in kind, noting that the toxicity of 2'-CDG to mammals compared to that non-toxicity of entecavir was more than a mere difference in degree. The post-filing evidence of 2'-CDG's high mammalian toxicity was an unexpected difference in *kind* to Judge Newman, whereas the federal circuit panel did not consider evidence of that toxicity. Rather, it viewed unexpected results based on a comparison between what was known about the toxicity of 2'-CDG at the time and the claimed entecavir.

Like Judge O'Malley, Judge Taranto's dissenting opinion sought to limit the reach of the panel opinion by clarifying what the panel opinion actually stated as compared to how it could likely be interpreted. For example, Judge Taranto stated that the panel opinion did *not* hold that evidence of unexpected results cannot by itself support a finding of nonobviousness, and it did not hold that *in vitro* experiments with a lead compound are sufficient evidence to establish a reasonable expectation of success. Lastly, without reaching any conclusions, Judge Taranto also stated that the panel's affirmance of the district court's decision not to consider 2'-CDG's later-discovered toxicity raised questions that warrant further exploration.

IV. DOES *BMS V. TEVA* REPRESENT A CHANGE IN THE LAW ON THE USE OF POST-INVENTION EVIDENCE IN THE OBVIOUSNESS ANALYSIS?

Neither the district court, nor the federal circuit panel, nor eight out of twelve federal circuit judges thought *BMS v. Teva* represented a change in the law that required *en banc* reconsideration. And there is ample support for their position. Both the district court and federal circuit opinions amply cite to federal circuit and C.C.P.A. precedent regarding the use of post-invention evidence. There is, however, an important difference between how post-invention evidence of high toxicity was argued by BMS and considered by the district court and the federal circuit panel on the one hand, and how dissenting court members and industry critics have interpreted the resulting decisions on the other.

a. Consideration of 2'-CDG's toxicity in lead compound selection

Both the district court and the federal circuit panel in fact considered the toxicity of 2'-CDG in the analysis of whether it would have been chosen as lead compound. Both courts considered, e.g., the Shealy (1984), Montgomery (1989), and Bennett (1990) articles, which either did not report any toxicity problems or that the toxicity was not significant in comparison to the efficacy of the compound.¹⁸ The district court also cited to the testimony of the BMS' expert who did not address toxicity in the context of the prior art references. The district court concluded that in view of all of the teachings in the prior art available to a POSA in 1990, speculative toxicity data would not have dissuaded that person from choosing 2'-CDG as a lead compound.

The district court and the federal circuit panel did not consider post-filing evidence of 2'-CDG's toxicity because it was not known at the time of invention and

could not have influenced the selection of a lead compound by a POSA. The district court specifically acknowledged that courts may consider later discovered evidence in the context of evaluating unexpected results (a secondary consideration), but that *prima facie* obviousness was focused “squarely on the time period in which the invention occurred.”¹⁹ The federal circuit panel confirmed that the proper focus is on the prior art “at the time of invention” when considering candidates for a lead compound. The court’s reasoning was firmly premised upon the proscriptions against the use of “hindsight” bias in determining whether a compound would have been obvious: after all, if hindsight knowledge cannot be used to construct a claimed compound from elements of the prior art, it cannot logically be used to teach away from the combination of prior art elements where there is reason or motivation to combine their teachings.

Because the “persons of ordinary skill in the art” and “lead compound” analyses are hypothetical constructs based upon omniscient knowledge at a fixed point in time, they would seem best served by the federal circuit’s approach of considering only the information available at the time of invention. If it were otherwise, the compound(s) selected as the lead compound(s) would inherently vary according to the timing of any litigation and the information then available about the prior art compounds.

b. Consideration of 2’-CDG’s toxicity in determining whether there existed a reasonable expectation of success

A *prima facie* case of obviousness requires motivation to make a change to a lead compound combined with a reasonable expectation of success of the resulting compound. Teva argued that a reasonable expectation of success would have been based on the good antiviral activity of 2’-CDG at the time of invention and a favorable toxicity profile. At the time of invention, the relevant literature reported a toxicity for 2’-CDG that was well above its therapeutic window for efficacy. But BMS did not appear to rely on the post-filing evidence of toxicity in arguing ‘no reasonable expectation of success,’ and the district court emphasized BMS’ failure to address that evidence in any great detail, and how, if at all, that factor would have negated the establishment of *prima facie* obviousness.²⁰ But given the federal circuit’s recognition that “the skilled artisan’s reasonable expectation of success is measured ‘as of the date of the invention,’” it is doubtful whether BMS could have done so.²¹

c. Consideration of 2’-CDG’s toxicity in evaluating secondary considerations

The parties and *amici* debate whether *BMS v. Teva* has now foreclosed the use of post-filing evidence in evaluating secondary considerations of nonobviousness. In the U.S., courts may consider later-discovered differences between the prior art and the claimed invention in their obviousness inquiry.²² The district court considered toxicity in the context of safety and efficacy in determining whether entecavir demonstrated any unexpected results over the prior art. In so doing, the court considered post-filing evidence of its extraordinary potency against the hepatitis B virus, its very high genetic barrier to resistance, and that it was a very safe and effective drug.²³ Although the court

considered some of these discoveries unexpected and others not unexpected, the district court concluded they did not outweigh the strong *prima facie* case of obviousness.

The federal circuit affirmed these conclusions, which relied in part on post-invention evidence. Thus, neither the district court nor the federal circuit purported to change the law permitting consideration of post-invention evidence when evaluating secondary factors. To the contrary, the district court and federal circuit panel relied upon such evidence in reaching their conclusions. As Judge O'Malley stated in her concurrence, "[t]here is a distinction between limiting the obviousness inquiry to pre-invention evidence and finding post-invention evidence unpersuasive." Neither the district court nor the federal circuit limited the evidence of secondary considerations to that which was known only in the prior art.

d. Concerns raised by industry in response to the Federal Circuit's BMS opinion

Industry critics charge that the new standard applied by the district court "threatens settled expectations regarding obviousness," and will have a "devastating effect" on patent protection in the pharmaceutical field.²⁴ They argue that post-invention evidence must be considered in an obvious analysis. They are correct -- post-invention evidence will be considered in an obvious analysis going forward because *BMS v. Teva* did not change the law in that regard.

But there is a difference in considering whether post-filing evidence can be used in determining whether a POSA would have had a reasonable expectation of success after selecting and modifying a lead compound, and whether that evidence can be used to show unexpected results as a secondary consideration to rebut a *prima facie* showing of nonobviousness. Some *amici* confuse the two.

The *BMS v. Teva* decisions did not consider post-filing evidence of 2'-CDG's toxicity in evaluating Teva's *prima facie* case of obviousness (selection of lead compound, reasonable expectation of success), because later demonstrated toxicity was not known at the time of the invention and could not have informed the lead compound selection, motivation to modify, or any expectation of success based thereupon. The courts *did* consider evidence of toxicity as an unexpected property as a secondary consideration in view of the safety and efficacy of entecavir. They concluded while some of the unexpected properties supported a finding of nonobviousness, others did not, and that the claimed entecavir would have been obvious based upon the totality of evidence before them.

Importantly, the post-filing evidence of toxicity related to the *prior art* compound, not the *claimed* compound entecavir. At the time of filing, 2'-CDG was believed to be safe, effective, and non-toxic. The fact that entecavir was also determined to be safe, effective, and non-toxic was not unexpected based on what was *then* known about 2'-CDG. None of the post-filing evidence altered what was known about the claimed entecavir, or what properties could have been reasonably expected *based on what was known at the time of filing*. Although the post-filing evidence of toxicity would have

altered the reasonable expectation of success, and also the selection of a lead compound, the improper use of hindsight would be required.

Perhaps much of the industry criticism from patent owners and innovator pharmaceutical companies may be a reaction to a rare determination by the federal circuit that a compound claim was invalid as obvious based on a structurally similar prior art compound. Although future litigants will doubtless seek to enlarge or diminish the actual holdings of these cases, the fact-specific nature of *BMS v. Teva* makes it unlikely that either case signals a changing trend in the judicial treatment of pharmaceutical compound claims.

V. CONCLUSION: LOOKING FORWARD

The federal circuit has now more clearly defined the purposes for which post-filing evidence can be considered in an obviousness inquiry. *BMS v. Teva* makes clear that the hypothetical inquiries into the selection of a lead compound(s), the motivation to modify those compounds, and any reasonable expectation of success will be evaluated from the perspective of a POSA at the time of invention. Litigants seeking to use post-filing evidence that would alter conclusions derived from knowledge and expectations at the time of filing may be frustrated. Post-filing evidence of secondary considerations will still be considered after *BMS v. Teva* just as it was before. Litigants seeking to rely on post-filing evidence are advised to present that evidence in a way that courts will most favorably consider its impact on the obviousness analysis.

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

² *See Bristol-Myers Squibb*, 923 F. Supp. 2d 602 (D. Del. 2013).

³ *Bristol-Myers Squibb*, 769 F.3d 1339 (Fed. Cir. 2014).

⁴ *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). This two-step analysis also applies during prosecution of patent claim directed to a chemical compound. *See* MPEP § 2143.

⁵ *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

⁶ *Takeda Chem. Indus., Ltd. V. Alphapharm Pt., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

⁷ *Otsuka Pharm. Co., Ltd v. Sandoz, Inc.*, 678 F.3d 1280, 1293 (Fed. Cir. 2012) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*)); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

⁸ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-407 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

⁹ *Bristol-Myers Squibb*, 752 F.3d at 977 (citing *Kao Corp. v. Unilever US, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) and *Pfizer*, 480 F.3d at 1371).

¹⁰ The figures used in this article are reproduced from Teva Pharmaceuticals' Appeal Brief at pages 5, 6, and 16.

¹¹ The '244 patent at 3:62-4:34 describes the claimed compounds as exhibiting antiviral activity and are effective against viruses including herpes simplex virus 1 (“HSV-1”) and herpes simplex virus 2 (“HSV-2”).

¹² *Velander v. Garner*, 348 F.3d 1359, 1377 (Fed. Cir. 2003).

¹³ *In re Dillon*, 919 F.2d 688, 693 and 697 (Fed. Cir. 1990) (*en banc*).

¹⁴ *KSR Int’l Co.*, 550 U.S. at 416.

¹⁵ *In re Dillon*, 919 F.2d at 688,692.

¹⁶ *Bristol-Myers Squibb*, 752 F.3d at 976 (citing *Dillon*, 919 F.2d at 693, 697).

¹⁷ *Id.*

¹⁸ *Bristol-Myers Squibb*, 923 F. Supp. 2d at 661-662.

¹⁹ *Id.* at 662, n. 24 (citing *OSI Pharm., Inc. v. Mylan Pharm. Inc.*, 858 F. Supp. 2d 341, 355(D. Del. 2012)).

²⁰ *Id.* at 674.

²¹ *Bristol-Myers Squibb*, 752 F.3d at 976 (citing *Amgen Inc., v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009)).

²² *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014).

²³ *Bristol-Myers Squibb*, 923 F. Supp. 2d at 684-686.

²⁴ *See, e.g.*, briefs of *Amici Curiae* Intellectual Property Owners Association, 2014 WL 4079428, at *5 (July 28, 2014), and Pharmaceutical Research and Manufacturers of America, 2014 WL 4079429, at *7(July 28, 2014).

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