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# MISGUIDED PANIC AND MISSED OPPORTUNITY FOR PHARMACEUTICAL INVENTIONS: HOW UNEXPECTED RESULTS ECLIPSED REASONABLE EXPECTATION OF SUCCESS IN *BMS v. TEVA*

Christelle K. Pride<sup>†</sup>

In *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, the Federal Circuit missed an opportunity to clarify how courts should interpret “reasonable expectation of success” (RES) when assessing the nonobviousness of pharmaceutical and chemical inventions.<sup>1</sup> RES is when a person can predict that applying the prior art teachings will yield the desired invention.<sup>2</sup> Although 35 U.S.C § 103 of the Patent Act requires that courts evaluate RES from the perspective of the person having ordinary skill in the art (PHOSITA), the Federal Circuit often overlooks the PHOSITA’s viewpoint in nonobviousness inquiries.<sup>3</sup> The three-pronged nonobviousness test for pharmaceutical compounds is whether a PHOSITA would have selected the lead compound, had the motivation to change it to obtain the invention, and had a reasonable expectation of success in doing so. Therefore, by disregarding the determination of a PHOSITA specific to the field of the invention, and in turn what would be nonobviousness to such a person, courts essentially dilute the effectiveness of the nonobviousness test. Given the complexity and prohibitive cost of chemical inventions, a proper assessment of RES would incentivize innovation while rewarding only inventions that would not have occurred in the normal course of research.

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1. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.* (*BMS v. Teva, per curiam*), 769 F.3d 1339, 1341 (Fed. Cir. 2014) (per curiam).

2. *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

3. See Rebecca S. Eisenberg, *Obvious to Whom? Evaluating Inventions from the Perspective of PHOSITA*, 19 BERKELEY TECH. L.J. 885, 889–90 (2004); see also 3 MOY’S WALKER ON PATENTS § 9:50 (4th ed.) (pointing out that even in *Graham v. John Deere*, the case that introduced the level of skill in the art into the obviousness analysis, the Supreme Court failed to determine a PHOSITA); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1 (1966).

In *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals U.S.A, Inc.*, a Federal Circuit panel held that Bristol-Myers Squibb's patent for Entecavir, a drug used to treat chronic hepatitis B, was invalid under § 103.<sup>4</sup> Bristol-Myers Squibb (BMS) sued Teva Pharmaceuticals (Teva), alleging patent infringement.<sup>5</sup> The district court held that the patent was invalid as obvious under § 103.<sup>6</sup> On appeal, the Federal Circuit panel rejected an attempt by BMS to use post-filing evidence of the prior art compound's *in vivo* toxicity to challenge the lead compound selection and findings of motivation to combine.<sup>7</sup> BMS waived its argument with regard to RES.<sup>8</sup> Consequently, the court reasoned that Entecavir's only unexpected property, high genetic barrier to resistance, was insufficient to rebut Teva's showing of prima facie obviousness.<sup>9</sup> The pharmaceutical industry expressed concern about *BMS v. Teva* because it thought that the Federal Circuit was now rejecting post-invention data as evidence of unexpected results.<sup>10</sup>

Although the *BMS* court did not change the law on the admissibility of post-filing data, it missed an opportunity to clarify how trial courts should apply the existing standard for RES. Pharmaceutical inventions need strong patent protection to incentivize the costly and prolonged investment in research and development (R&D).<sup>11</sup> A precise determination of RES, based on an accurate assessment of the PHOSITA, would enable the allowance or validation of strong patents.

Following BMS's petition for rehearing or rehearing en banc, the court delivered a set of seemingly conflicting opinions that the pharmaceutical industry perceived to radically change the standard for nonobviousness.<sup>12</sup> BMS and the pharmaceutical industry expressed concern over the possible

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

5. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc. (BMS v. Teva)*, 923 F. Supp. 2d 602, 608 (D. Del. 2013), *aff'd*, *BMS v. Teva, panel decision*, 752 F.3d 967 (Fed. Cir. 2014).

6. *Id.*

7. *BMS v. Teva, panel decision*, 752 F.3d at 974–76.

8. *BMS v. Teva*, 923 F. Supp. 2d at 674 n.36.

9. *BMS v. Teva, panel decision*, 752 F.3d at 977–78.

10. *See* Brief of Amicus Curiae Biotechnology Industry Organization Association in Support of Rehearing en Banc at 1, *BMS v. Teva, panel decision*, 752 F.3d 967 (Fed. Cir. 2014) (No. 14-886), 2015 WL 763993.

11. *See* Brief of Amicus Curiae Biotechnology Industry Organization Association in Support of Rehearing en Banc at 1, *BMS v. Teva, panel decision*, 752 F.3d 967 (Fed. Cir. 2014) (No. 14-886), 2015 WL 763993.

12. *BMS v. Teva, per curiam*, 769 F.3d at 1341.

prohibition of post-invention evidence to establish unexpected results and the undue limitation of the types of results that qualify as unexpected.<sup>13</sup>

This Note argues that the court overlooked an issue that is especially relevant to chemical and pharmaceutical inventions: the realistic assessment of “reasonable expectation of success.” In view of the complexity and unpredictability of the chemical arts, courts should narrowly define RES to incentivize innovation while rewarding only inventions that would not have arisen in the normal course of research. Part I describes the evolution of the nonobviousness doctrine and its application to the pharmaceutical and chemical arts. Part II summarizes the Federal Circuit’s decision in *BMS v. Teva*. Part III analyzes the court’s ruling and explains why *BMS v. Teva* did not change precedent on the use of post-filing evidence to establish unexpected results. Part IV examines the court’s missed opportunity to review the standard for reasonable expectation of success.

## I. INTRODUCTION TO THE NONOBVIOUSNESS INQUIRY AND ITS APPLICATION TO THE CHEMICAL AND PHARMACEUTICAL ARTS

United States patent law requires that patentable inventions be nonobvious in view of the prior art.<sup>14</sup> This Part describes the origins of the nonobviousness doctrine and examines the application of § 103 to pharmaceutical and chemical inventions.

### A. EVOLUTION OF THE NONOBVIOUSNESS REQUIREMENT OF PATENTABILITY

Two landmark events have shaped the development of the nonobviousness requirement for patentability: Congress’s passage of the Patent Act in 1952, and the Supreme Court’s decision in *Graham v. John Deere* in 1966.

#### 1. *The Statutory Test for Nonobviousness*

To incentivize the “Progress of Science and useful Arts,” Article I, Section 8, Clause 8 of the Constitution grants to inventors the exclusive

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13. *Id.* at 1341 (BMS’s petition for rehearing or rehearing en banc was filed along with amicus briefs from the Biotechnology Industry Organization, the Bay Area Bioscience Association, Pfizer, Inc., Eli Lilly & Co., the Pharmaceutical Research and Manufacturers of America, the Intellectual Property Owners Association, and Merck Sharp & Dohme Corp.).

14. *See* *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966) (stating that an invention requires a “degree of skill and ingenuity” (citing *Hotchkiss v. Greenwood*, 52 U.S. 248, 267 (1850))).

rights to their works for a limited period of time.<sup>15</sup> In 1851, the Supreme Court introduced nonobviousness into the judicial determination of patentability by stipulating that an invention required “more ingenuity and skill” than were possessed by an “ordinary mechanic acquainted with the business.”<sup>16</sup> In the Patent Act of 1952, Congress codified the requirement for nonobviousness:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.<sup>17</sup>

Over the years, the Supreme Court has shaped the interpretation of § 103 nonobviousness through seminal decisions, notably, *Graham v. John Deere*<sup>18</sup> and *KSR Int'l Co. v. Teleflex Inc.*<sup>19</sup> In *Graham*, the Court described the factual inquiries that inform the obviousness analysis.<sup>20</sup> Several decades later, in *KSR*, it rejected the rigid application of the Federal Circuit’s Teaching, Suggestion, and Motivation (TSM) test<sup>21</sup> and espoused a more flexible approach that bars the patentability of inventions that are predictable variations of the prior art.<sup>22</sup>

## 2. *The Nonobviousness Requirement in Graham v. John Deere*

Nonobviousness is a question of law based on several factual inquiries called the *Graham* factors.<sup>23</sup> Under § 103, a fact finder must determine the scope and content of the prior art, assess the differences between the prior art and the invention, and evaluate the level of ordinary skill in the pertinent art.<sup>24</sup> Further, to ascertain the circumstances existing when the invention was made, the fact finder might evaluate secondary considerations such as commercial success, long felt but unresolved needs, and the failure of

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15. U.S. CONST. art. 1, § 8, cl. 8.

16. *Hotchkiss v. Greenwood*, 52 U.S. 248, 267 (1850).

17. 35 U.S.C. § 103 (1952).

18. *Graham*, 383 U.S. at 17.

19. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

20. *Graham*, 383 U.S. at 17.

21. *KSR*, 550 U.S. at 415.

22. *Id.* at 417.

23. *Graham*, 383 U.S. at 17.

24. *Id.*

others.<sup>25</sup> Although *Graham* established the factual framework that guides the legal inquiry of nonobviousness, it did not provide bright-line rules for determining nonobviousness.<sup>26</sup>

Furthermore, *Graham* merely introduced the concept of secondary considerations, leaving lower courts to expound additional categories of secondary considerations such as copying,<sup>27</sup> professional approval or skepticism,<sup>28</sup> and unexpected results.<sup>29</sup> By adding secondary considerations to the nonobviousness analysis, the *Graham* Court intended that these “objective indicia” guard against hindsight bias by illuminating the context within which the invention was made.<sup>30</sup> This is because secondary considerations emphasize “economic and motivational, rather than technical issues, and are therefore more susceptible of judicial treatment than are the highly technical facts often present in patent litigation.”<sup>31</sup>

Although the Federal Circuit ruled soon after its creation<sup>32</sup> that evidence of secondary considerations “must always when present be considered en route to a determination of obviousness,”<sup>33</sup> there has been no uniform or regular application of secondary considerations.<sup>34</sup> While some courts examine several secondary indicia, others merely acknowledge the existence of these criteria by citing to *Graham*.<sup>35</sup>

## B. THE NONOBVIOUSNESS INQUIRY IN THE CHEMICAL ARTS

Although the § 103 requirement of patentability applies to all arts, the development of chemical and pharmaceutical inventions has some unique

25. *Id.*

26. See Justin Lee, Note, *How KSR Broadens (Without Lowering) the Evidentiary Standard of Non-Obviousness*, 23 BERKELEY TECH. L.J., 15 (2008); see also *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1567–68 (Fed. Cir. 1987) (supplementing the *Graham* fact inquiries with legal questions and legal standards for fact-finding).

27. *Janssen Pharmaceutica N.V. v. Mylan Pharm. Inc.*, 456 F. Supp. 2d 644, 669 (D.N.J. 2006).

28. See Natalie A. Thomas, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following KSR v. Teleflex*, 86 N.Y.U. L. REV. 2070, 2078 (2011).

29. See *id.* at 2078–79.

30. See *id.* at 2075–76.

31. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966).

32. Congress formed the Federal Circuit in 1982, and the ruling on secondary considerations was issued in 1983.

33. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

34. See Thomas, *supra* note 28, at 2084–85 (mentioning a survey of district court and Federal Circuit opinions that revealed that secondary considerations were sufficient to overcome a prima facie case of nonobviousness in a single case out of ninety-three).

35. See Jonathan J. Darrow, *Secondary Considerations: A Structured Framework for Patent Analysis*, 74 ALB. L. REV. 47, 51 (2011).

attributes. This Section examines some of these attributes and presents how courts apply § 103 to the chemical arts.

1. *Particularities of Chemical and Pharmaceutical Inventions*

First, the lengthy and costly drug development process increases the importance of patents to the pharmaceutical industry. Drug development is the process of taking a candidate drug from identification to marketing approval by the United States Food and Drug Administration (FDA).<sup>36</sup> On average, the development of an approved drug takes ten to fifteen years and costs \$1.5 billion.<sup>37</sup> Pharmaceutical companies depend on patents for a period of market exclusivity during which they can recoup their investment.<sup>38</sup> Therefore, securing a patent for a pharmaceutical or chemical invention is even more important than it is in most other industries.

At the same time, overcoming nonobviousness is particularly difficult for pharmaceutical and chemical inventions.<sup>39</sup> This is because in those fields, innovation often begins with modifying known compounds by trial and error and then testing the products until one with the desired properties is obtained.<sup>40</sup> Small changes at the molecular level can yield significantly different products.<sup>41</sup> This process is unlike what happens in the mechanical arts, which tend to include less micro-scale modification of existing devices. Consequently, pharmaceutical and chemical inventions are highly susceptible to a finding of obviousness-to-try.<sup>42</sup>

2. *Nonobviousness Analysis for Chemical and Pharmaceutical Inventions*

Presently, courts assess the obviousness of chemical compounds by focusing on the identification of a lead compound, which is a compound in the prior art that would be “a natural choice for further development

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36. See, e.g., Henry Grabowski, *Patents, Innovation, and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849, 851 (2002).

37. See Michael Enzo Furrow, *Pharmaceutical Patent Life-Cycle Management After KSR v. Teleflex*, 63 FOOD & DRUG L.J. 275, 278, 283 (2008).

38. *Id.* at 278.

39. See Kristen C. Buteau, *Deuterated Drugs: Unexpectedly Nonobvious?* 10 J. HIGH TECH. L. 22, 23 (2009).

40. *Id.*

41. See Andrew V. Trask, “*Obvious-to-try.*” *A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625, 2626 (2008) (using the thalidomide story to illustrate how chemically identical but spatially different molecules can have drastically different biological effects).

42. See Jonathan M. Spenner, *Obvious-to-Try Obviousness of Chemical Enantiomers in View of Pre- and Post-KSR Analysis*, 90 J. PAT. & TRADEMARK OFF. SOC'Y. 475, 477 (2008).

efforts.”<sup>43</sup> This Section examines the § 103 test for chemical inventions and introduces two principles of nonobviousness, “obvious-to-try” and “teaching away.”

To carry out a lead compound analysis (LCA), the nonobviousness test for chemical compounds, a court must determine:

- (a) Whether an artisan of ordinary skill would have selected the asserted prior art as starting point or lead compound;<sup>44</sup>
- (b) Whether the prior art would have provided the PHOSITA with the motivation to alter the lead compound to obtain the claimed compound;<sup>45</sup> and
- (c) Whether the PHOSITA would have had a reasonable expectation of success in making the invention.<sup>46</sup>

Over the years, the Federal Circuit’s decisions have provided practical guidelines for conducting a lead compound analysis. For instance, the selection of a lead compound must be based upon the compound’s pertinent properties such as activity, potency, and toxicity.<sup>47</sup> In general, a compound with better activity than the other candidates will likely be the choice.<sup>48</sup> Additionally, a small and finite number of lead compounds can be advantageous in convincing a court that a PHOSITA would have selected a certain lead compound.<sup>49</sup>

Once a lead compound has been established, the party contending that the patent is obvious can prove motivation to modify this compound through explicit references in the prior art.<sup>50</sup> In the absence of a specific teaching, courts can find a motivation to alter the lead compound by looking at the prior art as a whole.<sup>51</sup>

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43. *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

44. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

45. *Id.*

46. *Id.*

47. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012).

48. *See Takeda*, 492 F.3d at 1357; *see also Altana*, 566 F.3d at 1008 (finding that a disclosed compound, compound 12, was the clear choice for further development because it had a higher potency than any of the other compounds, and even though there were concerns about its toxicity).

49. *Ortho-McNeil Pharm. Inc. v. Mylan Lab., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2009).

50. *Altana*, 566 F.3d at 1008.

51. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1352 (Fed. Cir. 2007).



Finally, the patent challenger must show that “as of the date of the invention,” a PHOSITA would have had a reasonable expectation of success in modifying the lead compound.<sup>52</sup> This is the third prong of the *prima facie* obviousness inquiry for chemical compounds. It has been recognized for a long time and occupies the middle ground between “absolute predictability” and a “general incentive” to pursue a course of research.<sup>53</sup>

In addition to the LCA, courts sometimes use two principles of nonobviousness: obvious-to-try and teaching away. In *KSR*, the Supreme Court rejected the Federal Circuit’s assertion that “a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try.”<sup>54</sup> An invention would likely be obvious where there was a “design need or market pressure to solve a problem,” and a PHOSITA had a “finite number of identified, predictable solutions” to try.<sup>55</sup>

Additionally, the Federal Circuit has extensively used the principle of “teaching away.” According to this rationale, an invention may be nonobvious if the prior art discouraged the solution that the inventor chose, or would have led a PHOSITA on a path that conflicts with the one the inventor selected.<sup>56</sup> The teaching away inquiry is a question of fact.<sup>57</sup> A reference that is silent and does not “criticize, discredit, or otherwise discourage” the invention claimed does not teach away.<sup>58</sup> Additionally, a reference that discloses several alternatives, and even emphasizes that the invention is not the best option, does not teach away unless it specifically discourages the inventor’s choice.<sup>59</sup> Furthermore, the obviousness inquiry must consider the totality of the prior art. When a single reference teaches away, yet others consistently point to the claimed invention, a finding of nonobviousness is not assured.<sup>60</sup>

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52. *Amgen Inc. v. Hoffman–La Roche*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

53. *See* Trask, *supra* note 41, at 2634–36.

54. *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 402 (2007).

55. *Id.*

56. *United States v. Adams*, 383 U.S. 39, 51 (1966).

57. *Para–Ordnance Mfg., Inc. v. SGS Imps. Int’l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995).

58. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *see also* *Para–Ordnance Mfg., Inc. v. SGS Imps. Int’l, Inc.*, 73 F.3d 1085, 1090 (Fed. Cir. 1995).

59. *See* *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355–56 (Fed. Cir. 2012) (citing *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (“A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.”)).

60. *See* *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165–66 (Fed. Cir. 2006).

## II. BMS V. TEVA

BMS sued Teva in the United States District Court for the District of Delaware for allegedly infringing its United States Patent No. 5,206,244 (“244 patent”).<sup>61</sup> At trial, Teva challenged the validity of the ’244 patent under § 103.<sup>62</sup> The district court held that Teva had demonstrated by clear and convincing evidence that the ’244 patent was invalid as obvious under § 103.<sup>63</sup> After reviewing the obviousness issue *de novo*, a Federal Circuit panel of three judges affirmed the district court’s finding of invalidity.<sup>64</sup> The Federal Circuit later denied BMS’s petition for rehearing and rehearing en banc, issuing two concurrences and two dissents.<sup>65</sup> This Part presents the facts of *BMS v. Teva* and reviews the district court and Federal Circuit rulings.

### A. THE FACTS OF *BMS V. TEVA*

In October 1990, BMS applied for the patent at issue, the ’244 patent.<sup>66</sup> The United States Patent and Trademark Office (USPTO) granted the patent in 1993.<sup>67</sup> Claim 8 was directed towards Entecavir, a compound developed to treat chronic hepatitis B virus infections.<sup>68</sup> Entecavir is a nucleoside analog, a compound created to mimic naturally occurring nucleosides that interfere with viral DNA replication.<sup>69</sup> Specifically, Entecavir is structurally similar to the natural nucleoside deoxyguanosine, with the substitution of an exocyclic methylene group (carbon-carbon double bond) for the oxygen in the five-membered ring (see Figure 1).<sup>70</sup>

At the time of Entecavir’s invention, 2’-CDG, another deoxyguanosine analog, existed in the prior art and was widely regarded as an effective antiviral agent (see Figure 1).<sup>71</sup> In 1989, published findings indicated that 2’-CDG had “excellent” *in vitro* activity against the hepatitis B virus and was effective at *in vitro* concentrations much lower than its toxic level.<sup>72</sup>

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61. *BMS v. Teva*, 923 F. Supp. 2d 602, 608 (D. Del. 2013), *aff’d*, *BMS v. Teva*, *panel decision*, 752 F.3d 967 (Fed. Cir. 2014).

62. *Id.*

63. *Id.*

64. *BMS v. Teva*, *panel decision*, 752 F.3d 967 (Fed. Cir. 2014).

65. *BMS v. Teva*, *per curiam*, 769 F.3d 1339 (Fed. Cir. 2014).

66. U.S. Patent No. 5,206,244 (filed Sep. 20, 1991).

67. *Id.*

68. *BMS v. Teva*, 923 F. Supp. 2d 602, 608 (D. Del. 2013), *aff’d*, *BMS v. Teva*, *panel decision*, 752 F.3d 967 (Fed. Cir. 2014).

69. *Id.* at 611.

70. *Id.* at 620.

71. *Id.* at 618–20.

72. *Id.* at 618.

However, *in vivo* studies conducted in the 1990s, after Entecavir's invention, revealed that 2'-CDG was unsafe in animals.<sup>73</sup>

In 2005, BMS obtained the FDA's approval to market Entecavir under the trade name Baraclude®.<sup>74</sup> In June 2010, Teva filed an abbreviated new drug application (ANDA) to market a generic version of Baraclude®.<sup>75</sup> The ANDA contained a Paragraph IV certification asserting that the '244 patent was invalid or unenforceable, and/or Teva's manufacture, use, or sale of Entecavir tablets would not infringe the '244 patent.<sup>76</sup> BMS then initiated a patent infringement suit against Teva in the United States District Court for the District of Delaware.<sup>77</sup>

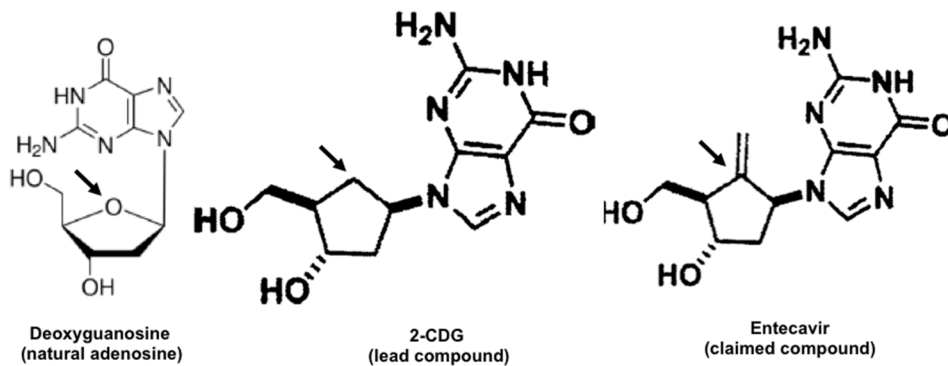


Figure 1: Molecular Structures of deoxyguanosine, 2'-CDG, and Entecavir: the arrows indicate the differences in molecular structure between the three compounds.

## B. THE DISTRICT COURT DECISION

The district court held that Teva had demonstrated by clear and convincing evidence that the '244 patent was invalid as obvious under § 103.<sup>78</sup> The court assessed Teva's *prima facie* case of obviousness and then evaluated objective considerations of nonobviousness.<sup>79</sup> It found a strong *prima facie* case because a PHOSITA would have found the selection of 2'-CDG as lead compound obvious and would have had a motivation to

73. *Id.* at 608.

74. *Id.*

75. *Id.*

76. *Id.*

77. *Id.*

78. *Id.* This Note does not discuss BMS's alleged inequitable conduct before the Patent and Trademark Office (PTO). The district court found that Teva had not met its burden of proof with regard to inequitable conduct, and the matter was not raised on appeal.

79. *Id.* at 686–87.

alter 2'-CDG to make Entecavir with a reasonable expectation of success.<sup>80</sup> Conversely, the court decided that evidence of secondary considerations (unexpected results, commercial success, and long-felt need) was not compelling.<sup>81</sup> Consequently, in light of Teva's persuasive and un rebutted prima facie arguments, the court held that claim 8 was invalid as obvious.<sup>82</sup>

### C. THE FEDERAL CIRCUIT DECISION

On appeal, the Federal Circuit issued opinions about *BMS v. Teva* on two occasions. First, a three-judges panel affirmed the trial court's finding of invalidity due to obviousness. Second, in the denial of BMS's petition for rehearing and rehearing en banc, the court released two concurrences and two dissents.

#### 1. Decision of the Three-Judge Panel

BMS appealed the district court's decision of invalidity to the Federal Circuit.<sup>83</sup> First, because 2'-CDG was discovered to be toxic after Entecavir's invention, BMS contested the lower court's finding that a PHOSITA would have selected 2'-CDG as lead compound and modified it to obtain Entecavir with a reasonable expectation of success.<sup>84</sup> Second, BMS contended that the district court had erred by holding Entecavir obvious in spite of evidence of unexpected results.<sup>85</sup> After reviewing the obviousness issue *de novo*, a panel of three judges affirmed the district court's ruling.<sup>86</sup>

With regard to BMS's first challenge, the judges found that since 2'-CDG's high toxicity was still unknown at the time of Entecavir's invention, researchers commonly used 2'-CDG as lead compound.<sup>87</sup> Given 2'-CDG's established antiviral properties and the pronounced structural similarities between 2'-CDG and Entecavir, the panel concluded that, at the time of the invention, a PHOSITA would have selected 2'-CDG and

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80. *Id.* at 654–74. The court found that at the time of Entecavir's invention, the prior art taught the selection of 2'-CDG as a lead compound with antiviral activity, and given the structural similarity between 2'-CDG and Entecavir, a skilled chemist would have had a reason to modify 2'-CDG to yield Entecavir with a reasonable expectation of success of creating an antiviral compound.

81. *Id.* at 686. In assessing the presence of unexpected results as an objective index of nonobviousness, the court found that some of Entecavir's attributes (high potency, large therapeutic window) were predictable at the time of its invention, whereas its high genetic barrier to resistance was unexpected.

82. *Id.*

83. *BMS v. Teva, panel decision*, 752 F.3d 967 (Fed. Cir. 2014).

84. *Id.*

85. *Id.*

86. *Id.*

87. *Id.* at 974.

modified its structure by making “small conservative changes” to obtain Entecavir, with a reasonable expectation of success.<sup>88</sup>

Additionally, on the issue of unexpected results, the panel contrasted a difference “in degree,” which is that of a known and expected property, to a difference “in kind,” which is a new attribute unlike the known attribute.<sup>89</sup> The court found that Entecavir’s only unexpected property, a high genetic barrier to resistance,<sup>90</sup> did not *per se* defeat an established motivation to modify 2'-CDG to yield expected beneficial antiviral activity.<sup>91</sup> Therefore, the panel upheld the trial court’s finding of invalidity due to obviousness.<sup>92</sup>

## 2. *Opinions from the Denial for Rehearing and Rehearing En Banc*

BMS further filed a petition for rehearing and rehearing en banc, which the court denied in October 2014 while issuing two concurrences and two dissents.<sup>93</sup> BMS and the amici raised two issues in their petition: (1) whether post-invention differences between the prior art and the claimed compound could be used to rebut a prima facie case of obviousness;<sup>94</sup> and (2) whether the panel had reduced the importance of unexpected results by distinguishing “differences in kind” from “differences in degree.”<sup>95</sup> BMS and the amici expressed concerns that the panel’s ruling would unduly bar evidence of unexpected results in the pharmaceutical context, even though it is common practice in the industry to conduct experiments after filing a patent application.<sup>96</sup> Furthermore, BMS and the amici argued that the distinction between difference “in degree” and “in kind” was unwarranted

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88. *Id.* at 975–76.

89. *Id.* at 977–78.

90. *Id.* at 978. A genetic barrier is the number of mutations before resistance to the drug occurs, leading to decreased efficacy.

91. *Id.* at 976 (reiterating the court’s finding in *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) that “an unexpected result or property does not by itself support a finding of nonobviousness”).

92. *Id.*

93. *BMS v. Teva, per curiam*, 769 F.3d 1339, 1341 (Fed. Cir. 2014). BMS’s petition was filed along with amicus briefs from the Biotechnology Industry Organization, the Bay Area Bioscience Association, Pfizer Inc., Eli Lilly & Co., the Pharmaceutical Research and Manufacturers of America, the Intellectual Property Owners Association, and Merck Sharp & Dohme Corp.

94. *Id.* at 1342.

95. *Id.* at 1344.

96. Dennis Crouch, *Proving Non-Obviousness with Ex-Post Experimental Evidence?* PATENTLYO (Oct. 21, 2014), <http://patentlyo.com/patent/2014/10/obviousness-experimental-evidence.html> [<https://perma.cc/HU7L-XSU2>] (last visited Feb. 15, 2016).

because the extent “to which a drug is safe and effective is measured as success and failure in the pharmaceutical industry.”<sup>97</sup>

First, the circuit judges who issued concurring and dissenting opinions appeared sharply divided on the criteria for using post-invention data in the obviousness analysis.<sup>98</sup> Judge Dyk, in the first concurring opinion to the denial of rehearing, strongly opposed considering Entecavir’s safety—relative to the later-found evidence of 2’-CDG’s toxicity—an unexpected result.<sup>99</sup> Judge Dyk cited, among other precedential cases, his dissent in *Genetics Institute LLC v. Novartis Vaccines and Diagnostics, Inc.*, where he stated that an unexpected result had to be “either contained in the specification or contemporaneously known to the inventors.”<sup>100</sup> In contrast, Judge O’Malley (concurring) and Judge Newman (dissenting) both cited to the majority opinion in *Novartis*, declaring that case law clearly permits the consideration of later-discovered differences between the prior art and the invention as evidence of unexpected results.<sup>101</sup> Importantly, Judge O’Malley sought to alleviate the concern BMS and amici expressed, that the panel’s decision had dramatically changed the obviousness standard for pharmaceutical cases.<sup>102</sup> Nonetheless, Judge O’Malley emphasized that while judicial precedent permits later-discovered differences between the prior art and the invention to prove *unexpected results*, such post-invention evidence is not necessarily sufficient to rebut the prima facie case of obviousness.<sup>103</sup> Consequently, the concurrence concluded that the circumstances of the case did not support BMS’s argument that post-invention differences between 2’-CDG and Entecavir would have eliminated a PHOSITA’s reasonable expectation of success at the time of Entecavir’s invention.<sup>104</sup>

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97. *Id.*; see also Brief of Amicus Curiae Bay Area Bioscience Association in Support of Petitioner at 10, *BMS v. Teva, per curiam*, 769 F.3d 1339 (Fed. Cir. 2014) (No. 14-886), 2015 WL 763993.

98. See *BMS v. Teva, per curiam*, 769 F.3d at 1341.

99. See *id.*

100. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1317–18 (Fed. Cir. 2011).

101. See *BMS v. Teva, per curiam*, 769 F.3d at 1342, 1348 (Fed. Cir. 2014).

102. *Id.* at 1342.

103. *Id.* at 1343.

104. *Id.* at 1344. In her dissenting opinion, Judge Newman was silent on BMS’s contention that the post-invention differences in toxicity between Entecavir and 2’-CDG would have changed a PHOSITA’s choice of lead compound and altered his motivation to create Entecavir from 2’-CDG with a reasonable expectation of success. Judge Newman argued instead, as conceded by Judge O’Malley, that post-invention differences between the prior art and the invention could be used to prove unexpected results.

Second, the circuit judges had conflicting opinions on the panel's use of differences "in kind" versus those "in degree" while assessing unexpected results. Judge O'Malley's concurrence discounted the distinction as nothing more than an illustration of how one can assess unexpected properties.<sup>105</sup> In contrast, Judge Newman argued that the difference between toxic 2'-CDG (in mammals) and safe Entecavir (in humans) was not merely one in degree.<sup>106</sup>

Finally, Judge Taranto's dissent was atypical in that it pointed out that the panel's ruling upset the meaning of expressions such as "reasonable expectation of success" and "unexpected results."<sup>107</sup> He urged for a comprehensive analysis of the doctrinal issues "that may bear on assessing the real-world consequences of one answer or another in an industry where research is especially expensive and uncertain."<sup>108</sup>

### III. ANALYSIS OF THE FEDERAL CIRCUIT'S DECISION IN *BMS V. TEVA*

In *BMS v. Teva* the Federal Circuit answered, albeit in a confusing way, two questions related to unexpected results: whether patentees could use later-discovered information to establish unexpected results, and what types of differences between the prior art and the claimed invention qualify as "unexpected results." However, the court failed to articulate a practical test for "reasonable expectation of success," one that would account for the PHOSITA's perspective in the narrow field to which the invention pertains.

#### A. *BMS V. TEVA* DOES NOT CHANGE THE STANDARD FOR THE ADMISSIBILITY OF POST-FILING EVIDENCE OF UNEXPECTED RESULTS

The concern BMS and the amici expressed that the outcome here created a new standard for unexpected results was unsubstantiated because the decision followed Federal Circuit precedent.<sup>109</sup> Nevertheless, the circuit

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105. *Id.* at 1345.

106. *Id.* at 1352.

107. *Id.* at 1353.

108. *Id.* at 1354.

109. *BMS v. Teva, per curiam*, 769 F.3d 1339, 1342–43 (Fed. Cir. 2014) (O'Malley, J.) (stating that "[o]ur case law clearly allows the consideration of later-discovered differences between the prior art and the invention"). Precedent where courts consider post-invention differences between the prior art and the invention when evaluating unexpected results includes: *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1317–18 (Fed. Cir. 2011); *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir.

judges issued concurrences and dissents to the court's denial of rehearing, which taken together seemed to obscure the standard for resolving future cases.<sup>110</sup> This Section begins by reviewing two precedential cases where the Federal Circuit credited post-filing differences between the prior art and the invention—arising specifically from newly uncovered facts about the prior art compound—as unexpected results.<sup>111</sup> Next, it examines why the pharmaceutical industry thought that the *BMS v. Teva* ruling endangered the future admissibility of post-invention data.

*Novartis* is the first of the two cases where the Federal Circuit accepted post-filing data about the prior art's shortcomings and credited the differences between the prior art and the claimed compound as unexpected results.<sup>112</sup> There, the court held that Novartis' recombinant protein had a structure that conferred unexpected binding ability, even though the importance of these structural features for binding and their absence from Genetics's prior art protein were not appreciated at the time of Novartis's invention.<sup>113</sup> Both patents were directed to a truncated form of Factor VIII, which is a blood-clotting protein that circulates in the blood in an inactive form and resists degradation by binding to a large protein called von Willebrand factor (vWF).<sup>114</sup> However, Genetics's protein lacked, and Novartis's protein had, structural portions of Factor VIII that were revealed,

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2013); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). The court does distinguish whether the differences between the prior art and the invention are the result of later-discovered properties of the prior art or those of the invention. *See BMS v. Teva, per curiam*, 769 F.3d at 1344 (O'Malley, J.) (stating that “[t]he panel’s decision to affirm the district court’s findings does not foreclose the possibility that post-invention evidence regarding the properties of either the invention or the prior art might be persuasive in the appropriate case”).

110. *BMS v. Teva, per curiam*, 769 F.3d at 1353 (Taranto, J.) (stating that “in affirming invalidity for obviousness on the recited facts, [the panel] may have dismissed postfiling discoveries of prior-art compounds’ true properties as categorically irrelevant to the statutory inquiry . . . or it may have merely rejected the particular postfiling evidence here as insufficient”).

111. This Note specifically highlighted cases that addressed later-discovered deficiency of the prior art compound because, as Judge Taranto remarked, the panel’s decision might be misunderstood as narrowly rejecting post-invention data about the prior art compound’s true properties. *Id.*

112. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1295 (Fed. Cir. 2011).

113. *Id.* at 1307–08. The majority in *Novartis* addressed Judge Dyk’s dissent arguments by emphasizing that “[a]lthough the § 103 analysis remains properly focused ‘at the time the invention was made,’ it would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application.” *Id.*

114. *Novartis*, 655 F.3d at 1295.



post-filing, to be critical for the protein's blood-clotting activity by virtue of its ability to bind vWF.<sup>115</sup> Genetics sued Novartis, asserting that the latter's claims were obvious in view of Genetics's patent.<sup>116</sup> The Federal Circuit affirmed the district court's finding that Novartis's claims were not prima facie obvious because the proteins claimed were structurally different from those in the prior art, and because Genetics had failed to establish a motivation for modifying the proteins to achieve Novartis's invention.<sup>117</sup> Additionally, the court agreed with the district court that the ability of Novartis's proteins to bind vWF was evidence of unexpected results, even if the importance of the binding region was not appreciated at the time of invention.<sup>118</sup> Consequently, the court held Novartis's claim nonobvious.<sup>119</sup>

Similarly, in *Leo Pharmaceutical Products, Ltd. v. Rea*, the Federal Circuit held that post-invention evidence that the prior art formulations caused significant degradation of the active ingredients was a "strong indication" that the new pharmaceutical composition was unexpected.<sup>120</sup> There, Galderma R&D challenged Leo Pharmaceuticals Products's ("Leo") patent, which taught the treatment of psoriasis using a storage-stable combination of vitamin D and corticosteroids in one formulation.<sup>121</sup> Although similar combination treatments existed in the prior art, none had confronted or solved the stability problems associated with combining vitamin D analogs and corticosteroids in a single formulation.<sup>122</sup> Leo's inventors recognized the storage stability problem and, after extensive testing of solvents taught by the prior art, discovered one, polyoxypropylene 15 stearyl ether ("POP-15-SE"), which enabled a storage stable combination of a vitamin D analog and a corticosteroid.<sup>123</sup> The Board of Patent Appeals and Interferences found that Leo's improved formulation was not unexpected to a PHOSITA because one reference provided a motivation to use POP-15-SE as a

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115. *Id.* at 1302.

116. *Id.* at 1302.

117. *Id.* at 1304.

118. *Id.* at 1307–08. The majority in *Novartis* addressed Judge Dyk's dissent arguments by emphasizing that "[a]lthough the § 103 analysis remains properly focused 'at the time the invention was made,' it would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application." *Id.*

119. *Id.*

120. *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

121. *Id.* at 1349.

122. *Id.* Vitamin D analogs are best stored in basic environments with a pH above eight, while corticosteroids are most stable in acidic milieu where the pH is between four and six.

123. *Id.*

solvent.<sup>124</sup> The Federal Circuit reversed the Board's ruling, holding that evidence submitted during reexamination, proving that the prior art formulations resulted in "significant degradation of the vitamin D analog and corticosteroid," supported a finding of unexpected results.<sup>125</sup> Therefore, as *Novartis* and *Leo* demonstrate, the Federal Circuit accepts post-invention differences between the prior art and the claimed compound when evaluating unexpected results, even when such differences merely stem from newly revealed deficiencies in the prior art.

Like in *Novartis* and *Leo*, where post-filing experimentation revealed crucial deficiencies in the prior art, thereby amplifying the difference between the prior art and the claimed invention, knowledge of 2'-CDG's toxicity magnified Entecavir's safety. In *Novartis*, Novartis capitalized on such a difference to successfully argue for a finding of unexpected results.<sup>126</sup> In contrast, in *BMS v. Teva*, BMS presented evidence of Entecavir's unexpected properties "almost as an afterthought."<sup>127</sup> BMS instead concentrated on the choice of 2'-CDG as lead compound, arguing that in view of 2'-CDG's later-found toxicity, a PHOSITA would not have selected the compound as starting point or had a motivation to modify it with a reasonable expectation of obtaining Entecavir.<sup>128</sup> In so doing, BMS focused on the wrong parts of the obviousness analysis: the lead compound selection, the motivation of the PHOSITA, and the reasonable expectation of success are all fixed at the time of the invention, whereas unexpected results can be supported by post-invention evidence. Therefore, the later-acquired evidence of 2'-CDG's toxicity could be used to rebut the prima facie case of obviousness, but not to avoid a finding of prima facie obviousness in the first place.

Along the same lines, Judge Taranto noted that the panel's decision could elicit two interpretations: (1) post-invention data of the prior art's true properties is not relevant to the obviousness analysis; or (2) the particular evidence in this case, 2'-CDG's toxicity, was insufficient to overcome a strong prima facie case of obviousness.<sup>129</sup> Precedent (*Novartis* and *Leo*) refutes the first interpretation. By default, and as Judge O'Malley stated, the second interpretation is what the panel intended.<sup>130</sup> However, the court's

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124. *Id.* at 1352.

125. *Id.* at 1349, 1354.

126. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307–08 (Fed. Cir. 2011).

127. *BMS v. Teva, per curiam*, 769 F.3d 1339, 1346 (Fed. Cir. 2014).

128. *BMS v. Teva, panel decision*, 752 F.3d at 974.

129. *BMS v. Teva, per curiam*, 769 F.3d at 1353.

130. *Id.* at 1343.

lack of justification for rejecting BMS's post-filing evidence, other than timing, likely explains the concern expressed by BMS and the amici.<sup>131</sup>

Furthermore, the industry's perception of *BMS v. Teva* might come from the underlying tension between obvious-to-try and unexpected results, which was addressed there with much disarray. Professor Mark Lemley has written about the conflict between obvious-to-try and unexpected results in the chemical arts.<sup>132</sup> He pointed out that post-*KSR*, courts have grappled to resolve the tension between obvious-to-try and unexpected results.<sup>133</sup> He remarked that when, as in *BMS v. Teva*, the prior art's shortcoming was unknown at the time the patent was filed, and a PHOSITA would be motivated to make simple changes to the prior art to arrive at the invention, unpredictable results do not make the invention nonobvious.<sup>134</sup> *Leo* supports Professor Lemley's thesis. The factual elements of *Leo* differ from those of *BMS v. Teva* in a significant way. Unlike *Leo*, who recognized the storage stability problem and sought to solve it with its pharmaceutical formulation, BMS had no pre-invention knowledge of 2'-CDG's *in vivo* toxicity.<sup>135</sup> This distinction means that *Leo*'s invention was not obvious-to-try to a PHOSITA, "who would not have thought to try at all because they would not have recognized the problem."<sup>136</sup> In contrast, BMS had little chance of proving, based on the record, that it had not merely followed a "finite number of identified, predictable solutions," including the pre-1990s knowledge of 2'-CDG's *non-toxicity*, to make Entecavir.<sup>137</sup> Therefore, under Professor Lemley's rationale, Entecavir's obviousness-to-try and the pre-filing knowledge of 2'-CDG's *non-toxicity* rendered all future evidence of unexpected results moot.<sup>138</sup> However, it is apparent from the judges' concurrences and dissents that the court did not want to offer a bright-line rule, choosing instead to limit the decision to the "circumstances of this case."<sup>139</sup> Additionally, the court indicated that although BMS waived the argument here, evidence of 2'-CDG's toxicity could have made the claims

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131. *Id.* at 1353.

132. See Mark A. Lemley, *Expecting the Unexpected* (unpublished manuscript) (on file with author).

133. See *id.* at 14.

134. *Id.*

135. *BMS v. Teva*, panel decision, 752 F.3d at 974.

136. See *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

137. See *id.*

138. But cf. Scott R. Conley, *Irrational Behavior, Hindsight, and Patentability: Balancing the "Obvious to Try" Test with Unexpected Results*, 51 IDEA 271, 306 (2011) (proposing that "unexpectedly superior results should always rebut a *prima facie* obviousness determination under the 'obvious to try' test").

139. See *BMS v. Teva*, *per curiam*, 769 F.3d 1339, 1341 (Fed. Cir. 2014).

of reasonable expectation of success “less credible.”<sup>140</sup> Further, Judge Taranto emphasized the important role that reasonable expectation of success should play in the obviousness inquiry, as discussed further in Section IV.A below.<sup>141</sup> Therefore, the *BMS v. Teva* ruling was very fact-specific, and larger questions such as the meaning of “unexpected results” and “reasonable expectation of success” remained unresolved, likely contributing to the pharmaceutical industry’s malaise.

B. *BMS v. TEVA* AFFIRMS THAT THE FEDERAL CIRCUIT DISTINGUISHES BETWEEN DIFFERENCES IN KIND AND THOSE IN DEGREE IN ITS ASSESSMENT OF UNEXPECTED RESULTS

*BMS v. Teva* highlights that the Federal Circuit views evidence of unexpected results as either “differences in kind” or “differences in degree” between the prior art and the invention.<sup>142</sup> The *BMS v. Teva* panel declared that “‘differences in degree’ of a known and expected property [were] not as persuasive in rebutting obviousness as differences in ‘kind’—i.e., a new property dissimilar to the known property.”<sup>143</sup> Using this standard, the court rejected BMS’s claims of unexpected properties with regard to high potency against hepatitis B and larger than expected therapeutic window because the results were expected in view of 2’-CDG’s properties and structural similarity to Entecavir.<sup>144</sup> However, Judge Newman’s dissent to the denial of rehearing en banc argued that precedent going as far back as the Court of Customs and Patent Appeals (CCPA) had found an unexpected improvement in physiological activity probative of nonobviousness.<sup>145</sup> The dissent explained that while there was no conspicuous point at which “an obvious difference in degree [became] an unobvious difference in kind,” consideration of the subject matter was important.<sup>146</sup> Using this rationale, it argued that the difference between 2’-CDG’s toxicity in mammals and Entecavir’s safety in humans qualified as more than “a mere difference in degree.”<sup>147</sup>

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140. *See id.* at 1343–44 (O’Malley, J.) (stating that *BMS v. Teva* “[did] not foreclose the possibility that post-invention evidence regarding the properties of either the invention or the prior art might be persuasive in the appropriate case”).

141. *See id.* at 1355–56.

142. *BMS v. Teva*, panel decision, 752 F.3d at 977.

143. *Id.* (using the definition of “difference in degree” from *In re Papesch*, 315 F.2d 381, 392 (C.C.P.A. 1963)).

144. *Id.* at 977–78.

145. *BMS v. Teva*, per curiam, 769 F.3d 1339, 1351 (Fed. Cir. 2014).

146. *Id.* at 1352.

147. *Id.*

Because a finding of unexpected results has the potential to obviate a ruling of obviousness over the prior art, this Note seeks to determine, by reviewing fifteen cases that invoked unexpected results, whether certain factors were likely to yield a difference in kind versus one in degree.<sup>148</sup> In addition, this Note analyzes those factors' probativeness of nonobviousness<sup>149</sup> by selecting cases that were decided post-*KSR* and which span the period from 2007 to 2015. Two-thirds of the selected cases have been appealed to the Supreme Court and denied certiorari. The remaining cases have been highlighted as important in a treatise or a law review article. The selected cases includes decisions about patents directed to drug substances (two), pharmaceutical formulations (ten), combination compositions (three) and a stereoisomer (one). The Appendix shows a summary of the findings.

Several trends emerge from the review. First, the prior art that taught away from the invention was a predictor of the type of differences that the court would credit as unexpected results probative of nonobviousness.<sup>150</sup> Second, for new chemical entities, differences in degree of safety (fewer side effects) led to a finding of nonobviousness.<sup>151</sup> Third, for formulations, differences in degree and those in kind could yield to a finding of obviousness or nonobviousness. Interestingly, the notable delineation between obviousness and nonobviousness appeared to be teaching away. Fourth, for combination treatments, differences in degree led to a finding of obviousness, while a difference in kind resulted in a finding of

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148. See *BMS v. Teva, panel decision*, 752 F.3d 967; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007); *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511 (Fed. Cir. 2012); *Hoffman-La-Roche, Inc. v. Apotex, Inc.*, 748 F.3d 1326 (Fed. Cir. 2014); *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952 (Fed. Cir. 2014); *Galderna Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013); *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293 (Fed. Cir. 2015); *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352 (Fed. Cir. 2011); *In re Cyclobenzaprine Hydrochloride Extended Release Capsule Patent Litig.*, 676 F.3d 1063 (Fed. Cir. 2012); *Cadence Pharms., Inc. v. Exela PharmSci, Inc.*, 780 F.3d 1364 (Fed. Cir. 2015); *Insite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853 (Fed. Cir. 2014); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346 (Fed. Cir. 2013); *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286 (Fed. Cir. 2013); *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008).

149. *Id.*

150. In five of the fifteen cases, the court held that the claimed invention was obvious over the prior art. See Appendix. Interestingly, in four of those five cases, the court did not find any evidence that the prior art taught away from the invention. *Id.* Conversely, in eight of the ten cases with a ruling of nonobviousness, the court found or affirmed the district court's judgment that the prior art taught away from the invention. *Id.*

151. See *Takeda*, 492 F.3d 1350; see also *In re Rosuvastatin*, 703 F.3d 511.

nonobviousness. The review suggests that prior art that teaches away from the invention rather than differences in kind or degree is predictive of nonobviousness.

Additionally, the review suggests that the court sometimes credits as unexpected results differences in degree between the prior art and the claimed compound that are statistically significant, quantifiable, or numerically substantial. For example, in *Senju Pharmaceutical Co. v. Lupin Ltd.*, the court found that the claimed benefits of a patented formulation were not statistically significant from those of the prior art, and hence, were obvious.<sup>152</sup> In contrast, in *Cadence Pharmaceuticals, Inc. v. Exela PharmSci, Inc.*, the court found that a method produced unexpected results because it yielded pharmaceutical formulations that remained stable for two years, compared to those of the prior art, which only lasted several months.<sup>153</sup> Similarly, the court in *Insite Vision, Inc. v. Sandoz, Inc.* found that a sixty-fold increase in the concentration of the active ingredient when administered topically compared to orally constituted unexpected results.<sup>154</sup> Finally, the *Galderma* court stated that differences in percentages are differences in degree rather than kind, “where the modification of the percentage is within the capabilities of one skilled in the art at the time.”<sup>155</sup>

Applying our findings to *BMS v. Teva*, we determine that the panel correctly found that Entecavir’s enhanced potency and larger than expected therapeutic window were expected properties, which only differed in degree from those of 2’-CDG.<sup>156</sup> Rather than teaching away from Entecavir, the prior art as a whole guided a PHOSITA towards the selection of 2’-CDG and its modification to yield a compound with equal or better features.<sup>157</sup> There is no indication that the court attempted, like in *Senju*, to weigh the statistical significance of the differences between Entecavir and 2’-CDG.<sup>158</sup> It simply affirmed the district court’s finding that high potency and a large therapeutic window were expected properties that were not on a spectrum of unexpectedness like the property at issue in *Cadence*.<sup>159</sup> In contrast, the court rightly credited Entecavir’s high genetic barrier to resistance as an

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152. *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015).

153. *Cadence*, 780 F.3d at 1376.

154. *Insite*, 783 F.3d. 853.

155. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

156. *BMS v. Teva, panel decision*, 752 F.3d at 977–78.

157. *Id.* at 975–76.

158. *See Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1350–51 (Fed. Cir. 2015).

159. *Cadence Pharms., Inc. v. Exela PharmSci, Inc.*, 780 F.3d 1364, 1376 (Fed. Cir. 2015).

unexpected result.<sup>160</sup> Therefore, the court concluded that there was not sufficient evidence of unexpected results to rebut a prima facie case of obviousness.

Lastly, with regard to other secondary objectives of nonobviousness, BMS's evidence of long-felt need and commercial success was not very robust. The court highlighted in *Leo* that the time gap between the prior art's teaching of the components and the eventual preparation of a successful composition "speaks volumes to the nonobviousness" of the patent.<sup>161</sup> In contrast, the *BMS v. Teva* court agreed with the district court that evidence of long-felt need was "of limited value to BMS."<sup>162</sup> The plaintiffs in *In re Rosuvastatin* emphasized the unpredictability that pervaded the field of statin development at the time of the invention, highlighting that at least five companies had abandoned their research efforts.<sup>163</sup> Here, BMS could not successfully claim the same, given the multiple researchers who used 2'-CDG as lead compound before Entecavir's invention, and the existence—before Entecavir's invention and FDA approval—of three other drugs for treating hepatitis B.<sup>164</sup> Therefore, although BMS protested the court's use of difference "in kind" or "in degree," the ruling was based on precedent.

In view of Federal Circuit precedent, this Note presents a few practical lessons derived from the review of several cases about unexpected results. First, given that evidence of teaching away can rebut a prima facie case of obviousness, patentees must dutifully catalog prior art that teaches away from the invention during research and development. In addition, they must emphasize, when possible, quantitative and statistically significant differences between the prior art and the claimed invention.

#### IV. *BMS V. TEVA'S* CAUTIONARY TALE AND ITS IMPLICATIONS

Although *BMS v. Teva* received considerable attention for the court's perceived curtailment of the types of post-filing evidence that patent applicants could use to prove nonobviousness, a more important aspect of the opinion concerns what the Federal Circuit failed to do: clarify the application of reasonable expectation of success.

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160. *BMS v. Teva, panel decision*, 752 F.3d at 977–78.

161. *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1359 (Fed. Cir. 2013).

162. *BMS v. Teva, panel decision*, 752 F.3d at 979.

163. *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517 (Fed. Cir. 2012).

164. *BMS v. Teva, panel decision*, 752 F.3d at 978–79.

A. *BMS v. TEVA* OVERLOOKED THE MISGUIDED APPLICATION OF REASONABLE EXPECTATION OF SUCCESS

BMS argued before the trial court that in view of 2'-CDG's toxicity in mammals, no medicinal chemist could have had a reasonable expectation of success from the selection of 2'-CDG as lead compound because it was uncertain whether the invention would be safe for human use.<sup>165</sup> The trial court rightly rejected that argument because, like the PHOSITA's selection of lead compound, reasonable expectation of success is ascertained at the time of the invention, and allowing later-acquired knowledge would lead to impermissible hindsight.<sup>166</sup> Further, BMS first touched upon the PHOSITA's reasonable expectation of success in its reply brief to the trial court, thereby effectively waiving the substantive value of the argument in this case.<sup>167</sup>

Nonetheless, as Judge Taranto recognized, a more pertinent issue about "reasonable expectation of success" is whether success refers to what "motivates the investment in research—an acceptable safety/efficacy profile."<sup>168</sup> Stating that the panel's decision was not precedent for proving "reasonable expectation of success," based only on *in vitro* experiments with the lead compound,<sup>169</sup> he proposed a more adequate standard: whether, at the time of the invention, a PHOSITA would have had the reasonable expectation that "the lead compound, 2'-CDG, would be acceptably safe in humans."<sup>170</sup> Such a particularized statement of the reasonable expectation of success would adequately account for a PHOSITA's practical perspective and strengthen the quality of patents while preserving the incentive to pursue R&D. The Note therefore recommends that courts more diligently ascertain the level of skill in the art as part of the nonobviousness inquiry.

The Patent Act of 1952 centers the nonobviousness inquiry on what a PHOSITA would have believed or expected at the time of the invention.<sup>171</sup> Consequently, implementation of the statute should help distinguish patent-worthy inventions from routine advances, while also capturing the research objectives of the ordinary inventor. However, it has been posited that in practice, courts have attributed a minor role to the PHOSITA when

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165. *BMS v. Teva, per curiam*, 769 F.3d 1339, 1343 (Fed. Cir. 2014).

166. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (stating that "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure").

167. *BMS v. Teva, per curiam*, 769 F.3d. at 1343–44.

168. *Id.* at 1355.

169. *Id.*

170. *Id.*

171. *See* 35 U.S.C. § 103.



determining nonobviousness and often gloss over this third prong of the *Graham* factors.<sup>172</sup> Nonetheless, the Federal Circuit's nonobviousness jurisprudence includes a few cases where the court's decision hinged upon whether the PHOSITA's perspective had been adequately considered.<sup>173</sup>

One of these cases is *Daiichi Sankyo Co. v. Apotex, Inc.*, where the Federal Circuit held that the district court's incorrect determination of the PHOSITA led to the exclusion of prior art that made the invention obvious and thereby "tainted [the district court's] obviousness analysis."<sup>174</sup> There, the patent covered a method of treating bacterial ear infections by topically administering an antibiotic into the ear.<sup>175</sup> The district court found that the PHOSITA "would have a medical degree, experience treating patients with ear infections, and knowledge of the pharmacology and use of antibiotics," concluding that such a person would be a pediatrician or a general practitioner.<sup>176</sup> Apotex, the patent challenger, argued that the PHOSITA was "a person engaged in developing new pharmaceuticals, formulations, and treatment methods, or a specialist in ear treatments such as an otologist, otolaryngologist, or otorhinolaryngologist who also has training in pharmaceutical formulations."<sup>177</sup> The Federal Circuit determined that the art was to make a compound to treat ear infections without damaging the patient's ear as a side effect and adopted Apotex's definition of a PHOSITA because animal testing to determine the antibiotic's toxicity was outside a pediatrician or general practitioner's training.<sup>178</sup> Therefore, the court held that Daiichi's method of treatment was obvious in view of a prior art reference that the district court had excluded because the article targeted "a highly, highly subspecialized physician . . . which would be the otologist or the ear doctor," and not a pediatrician or general practitioner.<sup>179</sup>

BMS could have used the Court's rationale in *Daiichi* to argue in its original brief that the PHOSITA was a medicinal chemist engaged in the synthesis of a compound aimed at treating a medical condition in humans. Dr. Slusarchyk, the medicinal chemist who created the synthetic pathway for Entecavir, testified that "toxicity data about nucleoside analogs that he was making 'wouldn't deter [him] from making more compounds in the

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172. See Eisenberg, *supra* note 3, at 889–90.

173. See *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007).

174. *Id.*

175. *Id.* at 1255.

176. *Id.* at 1256.

177. *Id.* at 1257.

178. *Id.*

179. *Id.* at 1257–58.

area to investigate further’ as he was a ‘medicinal chemist,’ not a ‘toxicologist.’<sup>180</sup> Such a perspective is shortsighted and not an accurate representation of a PHOSITA engaged in drug development. As the *Daiichi* court recognized, in the course of conducting research aimed at creating a medication, a PHOSITA does not divorce compound toxicity or safety from efficacy.<sup>181</sup> Commentators have pointed out that the use of research teams with personnel from various specialties, as in the pharmaceutical industry, could render the PHOSITA determination problematic.<sup>182</sup> However, to date, the Federal Circuit has not ruled on such a case.

In addition to reversing a district court’s PHOSITA determination, the Federal Circuit has at times denied a finding of obviousness where the patent challenger did not consider safety or efficacy when arguing that the PHOSITA would have had a reasonable expectation of success of making the invention.<sup>183</sup> For example, in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, the court found that the modified-release formulation of a muscle relaxant was nonobvious because there was no proof that a PHOSITA had enough information to create a therapeutic formulation with a reasonable expectation of success.<sup>184</sup> Similarly, in *Eli Lilly & Co. v. Teva Pharmaceuticals USA, Inc.*, the court found that animal studies data, which suggested that the active ingredient would not have sufficient bioavailability in humans, would have deterred a PHOSITA from using the compound with a reasonable expectation of success.<sup>185</sup>

Finally, another way in which the determination of the person of ordinary skill in the art affects the obviousness analysis is the failure of the selected “PHOSITA” to account for intricacies in the art of the invention, for example, by inferring drug safety in humans solely from *in vitro* test results. A fundamental principle of pharmacology and toxicology is that a compound that causes an effect in one mammalian species will likely do the

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180. *BMS v. Teva*, 923 F. Supp. 2d at 624.

181. *See Daiichi*, 501 F.3d at 1257.

182. *See, e.g.*, Douglas L. Rogers, *Federal Circuit’s Obviousness Test for Pharmaceutical Compounds: Gobbledygook?* 14 CHI.-KENT J. INTELL. PROP. 49 (2014).

183. *See* Matter of Application of Carroll, 601 F.2d 1184, 1185 (C.C.P.A. 1979); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).

184. *In re Cyclobenzaprine Hydrochloride Extended Release Capsule Patent Litig.*, 676 F.3d 1063, 1066 (Fed. Cir. 2012).

185. *Eli Lilly & Co. v. Teva Pharms, USA, Inc.*, 619 F.3d 1329, 1339 (Fed. Cir. 2010).

same in another species.<sup>186</sup> In contrast, as Judge Taranto highlighted in his opinion, *in vitro* tests are rarely predictive of human clinical trials.<sup>187</sup>

By carefully accounting for the PHOSITA's expertise in the above cases, the Federal Circuit rewarded the efforts of an inventor who had persisted along a research path that a PHOSITA was discouraged from pursuing. Therefore, a meticulous articulation of the PHOSITA helps achieve two main purposes of patent law. First, it promotes more innovation by rewarding the inventor who took a risk and pursued a research direction from which the prior art taught away. Second, it ensures that only inventions that would not occur in the routine course of research receive patents.

#### B. GREATER JUDICIAL CONSIDERATION OF THE PHOSITA WOULD FULFILL A POLICY GOAL OF PATENT LAW

The primary goal of patent law is to incentivize innovation. The purpose of the obviousness requirement is to ensure that only patent-worthy inventions are rewarded with a period of exclusivity.<sup>188</sup> The PHOSITA gives courts adaptability and allows determinations of obviousness in a variety of technologies.<sup>189</sup> Patent law relies on this legal construct because it makes sense to use as arbiter of nonobviousness a person that works in a certain art and understands the patent in the context of the prior art.<sup>190</sup> Limiting patents to inventions that are not obvious to the PHOSITA and would not have occurred in the normal course of experimentation helps advance innovation while preserving resources.<sup>191</sup> Without an assessment standard such as the PHOSITA, R&D would stall as competitors rushed to patent every incremental discovery, and the transaction costs from patent thickets would undermine further investment in innovation.<sup>192</sup> Additionally, viewing developments from the PHOSITA's perspective provides an

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186. See FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 646 (3d ed. 2011).

187. *BMS v. Teva*, per curiam, 769 F.3d 1339, 1355 (Fed. Cir. 2014) (citing Henry Grabowski, *Patents, Innovation, and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849, 849–51 (2002) (“[F]ewer than 1% of the compounds examined in the pre-clinical period make it into human testing.”); Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, NAT. BIOTECH. 40, 47 (Jan. 2014) (10.4 % of drugs entering human testing emerge as marketed drugs)).

188. See Eisenberg, *supra* note 3, at 886.

189. See Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology Specific?*, 17 BERKELEY TECH. L.J. 1155, 1190–91 (2002).

190. See *id.*; see also Eisenberg, *supra* note 3, at 886.

191. See Eisenberg, *supra* note 3, at 886.

192. See *id.*

additional safeguard against hindsight bias by anchoring the decision-maker's mind to the time of the invention rather than the present.<sup>193</sup>

Accurate determination of the PHOSITA is essential to the assessment of nonobviousness and patentability.<sup>194</sup> On one hand, aiming too low with the PHOSITA allows “undeserving” patents that protect noninventive concepts. On the other hand, aiming too high with the PHOSITA yields too many findings of obviousness on “deserving” inventions. Finding the right balance would promote stronger patents, in turn giving greater confidence to pharmaceutical companies and encouraging investment in R&D.

To achieve a balanced and precise determination of the PHOSITA, this Note recommends implementing a two-pronged approach. First, courts need to reinstate the statutory role of the PHOSITA as spelled out under § 103. Some scholars have pointed out that active judicial review has steadily overtaken what should be a PHOSITA-driven evaluation of obviousness at the time the invention was made.<sup>195</sup> A return to conducting the obviousness inquiry from the perspective of the PHOSITA would start in courts, including the Federal Circuit, which in recent years has placed high emphasis on non-technological evidence such as secondary considerations when conducting an obviousness analysis.<sup>196</sup>

However, the stakes are high by the time the PHOSITA's perspective is obtained in the course of litigation.<sup>197</sup> An even better way to ensure the adequate assessment of obviousness while avoiding litigation costs is to modify practices at the USPTO.<sup>198</sup> Patent examiners are often former practitioners whose perspective on what is cutting edge lags behind that of current practitioners.<sup>199</sup> Hence, some have suggested that the USPTO should consult with outside practitioners at an early stage of the examination process.<sup>200</sup> Peer review of obviousness issues, modeled on what

193. *See id.* at 885.

194. *See* Joseph P. Merea, *Just Who is the Person Having Ordinary Skill in the Art? Patent Law's Mysterious Personage*, 77 WASH. L. REV. 267, 277–78 (2002). Currently, the Federal Circuit uses six factors in determining the PHOSITA. These factors are: “(1) educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which inventions are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.” *Id.*

195. *See* Eisenberg, *supra* note 3, at 889–90; *see also* Timothy R. Holbrook, *Patents, Presumption, and Public Notice*, 86 IND. L.J. 779, 784–85 (2011).

196. *See* Eisenberg, *supra* note 3, at 893.

197. *See id.* at 899.

198. *See id.* at 899–90.

199. *See id.*

200. *See id.*

happens at some federal agencies, has also been proposed.<sup>201</sup> Ultimately, an approach that combines regulatory and judicial implementation of § 103 from the perspective of the PHOSITA would best fulfill Congress's mandate as spelled out in the Patent Act of 1952.

## V. CONCLUSION

The Federal Circuit's decision in *BMS v. Teva* was widely depicted as imposing an extra burden on the pharmaceutical industry by unduly prohibiting post-invention evidence of unexpected results. In reality, although the judges' opinions appeared contradictory, the court did not change the precedent on the admissibility of post-invention data. *BMS v. Teva* reiterated that post-filing differences between the prior art and the claimed compound could help establish evidence of unexpected results. Additionally, it maintained the Federal Circuit's pattern of distinguishing between results that are differences "in kind" and those that are "in degree." Although *BMS v. Teva* did not alter precedent, it missed the opportunity to clarify the application of "reasonable expectation of success." This Note recommends a return to an emphasis on the PHOSITA's perspective and accurate assessment of "reasonable expectation of success" because such an approach leads to strong patents and incentivizes pharmaceutical innovation.

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201. *See id.* at 900–01.

## APPENDIX

## Summary of Selected Cases, Organized by Patent Subject Area

New Chemical Entities					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Fed. Cir. Findings
Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc., 752 F.3d 967, (Fed. Cir. 2014)	Nucleotide analog for treating chronic Hepatitis B.	N/A	Failure to prove unexpected results; Evidence of long-felt need and commercial success not robust.	High potency (degree) Larger than expected therapeutic window (degree) High genetic barrier to resistance (kind).	Obvious
Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007)	The claimed compound, pioglitazone, is the active ingredient in Takeda's anti-diabetic drug.	The prior art taught away from using compound b as lead compound.	No prima facie of obviousness, therefore no consideration of objective indices.	Controls blood sugar in in patients with Type 2 diabetes with fewer side effects (degree).	Nonobvious
In re Rosuvastatin Calcium Patent Litigation, 703 F.3d 511 (Fed. Cir. 2012)	Rosuvastatin is one of several statin products that lower cholesterol production in the liver by inhibiting the enzyme HMG-CoA reductase.	The prior art taught a preference not for hydrophilic substituents but for lipophilic substituents at the C2 position.	"Obvious to try" negated by the general skepticism, failure of others, and the evidence of teaching away. Also, commercial success, long felt but unfilled need, and unexpected results.	Superior efficacy in lowering low-density (LDL) cholesterol and elevating high-density (HDL) cholesterol, and its reduced side effects, as compared with other commercial statins (degree).	Nonobvious

Formulation					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Hoffmann-La Roche Inc. v. Apotex Inc. 748 F.3d 1326 (Fed. Cir. 2014)	Once monthly oral dosage regimen of ibandronate to treat osteoporosis.	The prior art did not teach away from the invention.	The evidence of superior efficacy does not outweigh the motivation to try a monthly dose and the reasonable expectation of success with the monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected. (Difference in degree).	Increased bioavailability when administered orally (degree); Effectiveness in reducing fractures.	Obvious
Allergan, Inc. v. Apotex Inc., 754 F.3d 952 (Fed. Cir. 2014)	Method for the treatment of eyelash hair loss through topical application of bimatoprost.	The district court found no evidence of teaching away in the prior art.	Evidence of unexpected results not commensurate with the scope of the claims. No rebuttal of prima facie.	Spontaneous growth of longer and thicker eyelash hair (kind).	Obvious

Formulation					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Galderma Laboratories, L.P. v. Tolmar, Inc., 737 F.3d 731 (Fed. Cir. 2013)	Pharmaceutical composition with active ingredient at 0.3% concentration.	Reversed the district's court finding of teaching away.	No commercial success as objective criterion of non-obviousness. The comparable tolerability of 0.1% and 0.3% adapalene was unexpected in view of the prior art, but it was a difference in "degree."	Concentration that treats acne without concomitant increase in side-effects (degree).	Obvious
Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, (Fed. Cir. 2015)	Drug formulation to treat glaucoma and ocular hypertension.	Prior art taught away from using BAK at 200 ppm to minimize cytotoxicity issues Also taught that BAK would not improve permeability of bimatoprost, but might reduce it.	Claimed inventions exhibited unexpected results that differed in kind from prior art.	Improved permeability of bimatoprost while decreasing side effects (kind).	Nonobvious



Formulation					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Unigene Laboratories, Inc. v. Apotex, Inc., 655 F.3d 1352 (Fed. Cir. 2011)	New formulation (pharmaceutical nasal spray) to deliver FDA-approved active ingredient salmon calcitonin) to treat, among other things, post-menopausal osteoporosis.	Prior art taught away from using 20mM citric acid as a stabilizing agent in a liquid formulation with a salmon calcitonin active ingredient.		Increased blood delivery to the organs of interest (degree).	Thus, the “about 20.0 mM citric acid” limitation alone supports the district court’s grant of summary judgment of nonobviousness.
In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation, 676 F.3d 1063, (Fed. Cir. 2012.)	Modified-release formulation of skeletal muscle relaxants and method of relieving muscle spasms with the formulation.		Evidence of a long-felt need for an extended-release formulation and the failure of others to formulate one strongly support a conclusion of non-obviousness.	Relief of muscle spasms for longer periods of time (degree).	Nonobvious

Formulation					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Cadence Pharmaceuticals Inc. v. Exela PharmSci Inc., 780 F.3d 1364 (Fed. Cir. 2015)	Formulations and methods for making liquid acetaminophen.	Prior art either taught away from the path adopted by the patentee, or was not aware of the storage stability issues that the patentee addressed.	Method claimed attained unexpected stability compared to the one disclosed in the prior art (two years versus only several months).	Invention stable for 2 years before six months (degree).	Nonobvious
Insite Vision Inc. v. Sandoz, Inc. 783 F.3d 853, (Fed. Cir. 2014)	Methods of treating eye infections by the topical administration of azithromycin to the eye.	The district court concluded that the prior art would have directed persons of ordinary skill in the art away from the topical administration of azithromycin.	Unexpected results Long-felt need.	60-fold increase in the concentration of the active ingredient when administered topically compared to orally (degree).	Nonobvious

Combination Treatment					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.	Combination therapy for type II diabetes, using repaglinide and metformin.		Obvious to try; secondary consideration evidence of unexpected synergy (i.e., attempt to prove unexpected results) was not sufficient to overcome challenger's prima facie case.	Synergism (degree).	Obvious. "It was apparently well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy."

Combination Treatment					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286 (Fed. Cir. 2013)	Combination composition comprising about 0.2% brimonidine by weight and about 0.5% timolol by weight as the sole active agents, useful for treating glaucoma or ocular hypertension ('149 patent) method of reducing the number of daily topical ophthalmic doses of brimonidine administered topically to an eye of a person in need thereof for the treatment of glaucoma or ocular hypertension from 3 to 2 times a day <b>without loss of efficacy.</b>		Long felt need claims conclusory; unexpected results are not sufficient to outweigh the other evidence of obviousness as to the formulation claims.	Increased efficacy of the drug and a reduction in side effects (degree).	<b>Formulation obvious;</b> method of administration nonobvious.

Combination Treatment					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Leo Pharmaceutical Products, Ltd. v. Rea, 726 F.3d 1346 (Fed. Cir. 2013)	Pharmaceutical composition to treat psoriasis, consisting of a Vitamin D analog, a corticosteroid, and a solvent.	teaching away	An invention can be the recognition of the problem itself; commercial success, long-felt need.	First to recognize and fix deficiency in the prior art. (unknown) (kind).	Nonobvious

Enantiomer					
Case Name	Invention Type	Teaching Away	Secondary Considerations	Unexpected results	Federal Circuit Findings
Sanofi-Synthelabo v. Apotex, Inc. 550 F.3d 1075 (Fed. Cir 2008)	Pharmaceutical product having the common name clopidogrel bisulfate and used to inhibit the aggregation of blood platelets, and treat or prevent heart attacks and strokes.	Evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage racemization.	Rare "absolute stereoselectivity": "The dextro-rotatory enantiomer provided all of the favorable antiplatelet activity but with no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity."	Rare "absolute stereoselectivity."	Nonobvious