

2013

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Recommended Citation

Maria Doukas, *A Discussion of Unigene Laboratories, Inc. v. Apotex, Inc.: The Standard for Prima Facie Obviousness of Pharmaceutical Formulation Claims in a Post-KSR World*, 11 NW. J. TECH. & INTELL. PROP. 457 (2013).
<http://scholarlycommons.law.northwestern.edu/njtip/vol11/iss5/7>

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N O R T H W E S T E R N
JOURNAL OF TECHNOLOGY
AND
INTELLECTUAL PROPERTY

**A Discussion of *Unigene Laboratories, Inc. v. Apotex, Inc.*:
The Standard for *Prima Facie* Obviousness of Pharmaceutical
Formulation Claims in a Post-*KSR* World**

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A Discussion of *Unigene Laboratories, Inc. v. Apotex, Inc.*: The Standard for *Prima Facie* Obviousness of Pharmaceutical Formulation Claims in a Post-*KSR* World

By Maria Doukas*

I. INTRODUCTION

¶1 In *KSR International Co. v. Teleflex Inc. (KSR)*,¹ the Supreme Court addressed obviousness in patent claims but failed to set forth a clear test for determining obviousness, particularly in the area of pharmaceutical patents. In its ruling, the Court stated the following: (1) “the combination of familiar elements according to known methods is . . . obvious when it does no more than yield predictable results;”² (2) if, at the time of the invention, a known problem existed and the patent encompasses an obvious solution to that problem, then the patent is obvious;³ and (3) if “there is a design need or market pressure to solve a problem” with a “finite number of identified, predictable solutions,” then the implementation of these solutions is the product of ordinary skill in the art and common sense, and not innovation.⁴ However, post-*KSR* cases have demonstrated that uncertainty remains as to the application of this ruling. Further, as the disputed patent in *KSR* was a mechanical arts patent, there has been confusion as to how to apply this standard to pharmaceutical patents.

¶2 This uncertainty is exemplified by the Federal Circuit’s ruling in *Pfizer v. Apotex*.⁵ In this case, the Federal Circuit applied a strict reading of the standard set forth in *KSR* to hold that the pharmaceutical patent in question was obvious and therefore invalid. The court stated that because the problem the patent set out to solve was known at the time of the invention and an identified solution was available in the prior art, a person of ordinary skill in the art would use this known solution to render the patented solution obvious. This strict reading of *KSR* was problematic because it did not allow courts to evaluate secondary considerations when looking at the obviousness of the patent. Additionally the court disregarded the fact that the “known” solution was rarely used in the art. After *Pfizer*, it appeared that pharmaceutical patents would be subject to a strict reading of the *KSR* obviousness standard.

¶3 However, on August 25, 2011, the Federal Circuit in *Unigene Laboratories, Inc. v. Apotex, Inc. (Unigene)* departed from the strict reading of *KSR* it applied in *Pfizer* and

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¹ 550 U.S. 398 (2007).

² *Id.* at 416.

³ *Id.* at 419–20.

⁴ *Id.* at 402–03.

⁵ *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

instead set forth an enhanced standard for evaluating obviousness in pharmaceutical formulations.⁶ This standard looked at the functionality of one of the components of the pharmaceutical formulation to determine if the prior art rendered the formulation obvious.⁷ This enhanced standard was a departure from the standard the Federal Circuit applied in earlier pharmaceutical cases and may make it more difficult to invalidate pharmaceutical formulation claims as obvious. This Note argues that the Federal Circuit was correct in setting forth this enhanced standard.

¶4 This Note proceeds in four parts. Part II briefly discusses what constitutes obviousness in patent claims under 35 U.S.C. § 103. This part addresses how the Supreme Court ruled on obviousness in patent claims in two cases: *Graham v. John Deere Company*⁸ and *KSR*.⁹ Part III analyzes the Federal Circuit's decision in *Pfizer v. Apotex*.¹⁰ Part IV analyzes the Federal Circuit's decision in *Unigene* by examining the relevant facts of the case and the court's rationale in determining nonobviousness of the patent claims. Part V assesses the implications that *Unigene* will have on the future of pharmaceutical patents.

II. OBVIOUSNESS IN PATENT CLAIMS

¶5 The Constitution empowers Congress "To promote the Progress of . . . useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their . . . Discoveries."¹¹ One of the requirements Congress has imposed in order for an invention to be patentable is that the invention be non-obvious. This patentability condition of "nonobviousness" is codified in the 1952 Patent Act at 35 U.S.C. § 103. This section currently states:

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.¹²

¶6 Despite the codification of the standard for obviousness, there is still considerable uncertainty concerning the distinction between what is patentable and what is "obvious." Two important Supreme Court decisions, *Graham*¹³ and *KSR*,¹⁴ provide guidance regarding the standards for determining obviousness under § 103. Despite these cases, there remains ambiguity for determining obviousness.

⁶ 655 F.3d 1352 (Fed. Cir. 2011), *cert. denied*, 132 S.Ct. 1755 (2012).

⁷ *Id.* at 1364.

⁸ 383 U.S. 1 (1966).

⁹ 550 U.S. 398 (2007).

¹⁰ 480 F.3d 1349

¹¹ U.S. CONST. art I, § 8, cl. 8.

¹² 35 U.S.C.A. § 103 (West 2013) (as amended as to matters unrelated to obviousness by Leahy-Smith America Invents Act § 3(c), 125 Stat. at 287 (2011), effective 2013).

¹³ 383 U.S. 1 (1966).

¹⁴ 550 U.S. 398 (2007).

¶7 In *Graham*, the Court ruled that while the ultimate question of patent validity is one of law, there are four basic factual inquiries that must be made under § 103.¹⁵ The four factual inquiries include: (1) the scope and content of the prior art, (2) differences between the prior art and the claims at issue, (3) the level of ordinary skill in the pertinent art, and (4) any evidence of secondary factors.¹⁶ These secondary factors include: commercial success, long-felt but unsolved needs, and the failure of others.¹⁷ These factual inquiries provide an objective framework for determining obviousness under 35 U.S.C. § 103.¹⁸

¶8 The Court in *KSR* reaffirmed the factual inquiries set forth in *Graham* while attempting to set forth a clearer standard for determining obviousness. In *KSR*, Teleflex owned a patent that combined an adjustable automobile pedal with an electronic sensor.¹⁹ Teleflex sued KSR for patent infringement after KSR developed an adjustable pedal system that had similar features to those in the Teleflex patent.²⁰ In ruling on KSR's summary judgment motion, the U.S. District Court for the Eastern District of Michigan applied the "teaching, suggestion, or motivation" (TSM) test that the Federal Circuit had previously applied in determining obviousness to grant KSR summary judgment.²¹ Under the TSM test, a patent claim is obvious if the prior art, "the problem's nature, or the knowledge of a person" with "ordinary skill in the art reveals some motivation or suggestion to combine the prior art" to teach the patent claims.²²

¶9 The district court applied the *Graham* factors to determine that there was "little difference" between the prior art and the patent claim at issue.²³ Because of this, the court ruled that the TSM test was satisfied. It reasoned that development within the industry would inevitably lead to the combination of sensors with adjustable pedals and the prior art provided the necessary basis for this combination.²⁴ Thus, the district court held the patent invalid.

¶10 However, on appeal, the Federal Circuit reversed the district court ruling, finding that the court had not applied the TSM test strictly enough and that there were genuine issues of material fact that precluded summary judgment.²⁵ The Federal Circuit reasoned that the prior art must address "the precise problem that the patentee was trying to solve."²⁶ Therefore, as the prior art references at issue did not address the problem the Teleflex patent was trying to solve, a person of ordinary skill in the art would not have looked to these references to design the pedal as claimed.²⁷ The court noted that even if it might have been obvious to combine the prior art references to form the pedal in the

¹⁵ *Graham*, 383 U.S. at 17.

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ MPEP § 2141(II) (8th ed. Rev. 9, Aug. 2011).

¹⁹ 550 U.S. at 399.

²⁰ *id.*

²¹ *id.*

²² *Id.*

²³ *Id.* at 400.

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.*

²⁷ *Id.*

patented claim, this was irrelevant because the problem at issue in the Teleflex patent was not addressed in this prior art.²⁸

¶11 The Supreme Court reversed the Federal Circuit’s decision, holding that the Federal Circuit applied a rigid, overly narrow test that was inconsistent with § 103 and the Court’s precedents.²⁹ In its ruling, the Supreme Court made several observations that have had implications on subsequent patent infringement cases in regards to finding obviousness.

¶12 First, the Court held that the “combination of familiar elements according to known methods is obvious when it does no more than yield predictable results.”³⁰ The Court reasoned that if “a work is available in one field of an endeavor [then] design incentives and . . . market forces [would] prompt variations of it.”³¹ Therefore, if a person of ordinary skill in the art could implement a predictable variation, then § 103 bars its patentability.³² Most importantly, the Court stated that, “the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.”³³

¶13 Second, the Court held that although the TSM test still has value, it should not be applied in the strict and rigid manner that the Federal Circuit had applied it. The Court ruled that it is not the particular motivation or the avowed purpose of the patentee that controls, but is instead the objective reach of the claim that matters.³⁴ The Court stated that if, at the time of the invention, a known problem existed and the patent’s claims encompass an obvious solution, then the patent’s subject matter can be proven obvious.³⁵ The Court noted that the Federal Circuit applied too strict a standard by holding that a person of ordinary skill in the art would look only to prior art designed to solve the same problem as the patent.³⁶ The Court observed that “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton.”³⁷ Therefore, even if the prior art was not designed to solve the particular problem of the patent, this does not preclude it from being used to prove obviousness.

¶14 Finally, the Court held that the Federal Circuit erred in finding that “a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try.”³⁸ The Court noted that if “there is a design need or market pressure to

²⁸ *Id.*

²⁹ *See id.*

³⁰ *Id.* at 401; *see also* Sakraida v. Ag Pro, Inc., 425 U.S. 273, 282 (1976) (holding that when a patent “simply arranges old elements with each performing the same function it had been known to perform” and yields no more than one would expect from such an arrangement, the combination is obvious); *United States v. Adams*, 383 U.S. 39, 51–52 (1966) (ruling that if elements in a patent work together in an unexpected and fruitful manner, the patent is non-obvious even if the patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field).

³¹ *KSR*, 550 U.S. at 417.

³² *Id.*

³³ *Id.* at 418.

³⁴ *Id.* at 419.

³⁵ *Id.* at 420.

³⁶ *Id.*

³⁷ *Id.* at 421.

³⁸ *Id.* at 402.

solve a problem and there are a finite number of indentified predictable solutions, [then] a person of ordinary skill in the art has [a] reason to pursue known options within his technical grasp.”³⁹ Therefore, the implementation of one of these predictable solutions would be the product of ordinary skill and common sense, not the product of innovation.⁴⁰

¶15 Despite the Supreme Court’s attempt to set forth a clearer standard for determining obviousness in *KSR*, its opinion instead resulted in more confusion among practitioners about the obviousness standard. This confusion is particularly acute in the area of pharmaceutical patents. Because *KSR* involved a mechanical arts patent, it is unclear how its holding should apply in the context of pharmaceutical patents.

¶16 One source of this confusion is the inherent difference between patents directed towards mechanical arts, such as the patent in question in *KSR*, and patents directed towards pharmaceuticals. For example, patents directed towards pharmaceuticals tend to be more complex and more unpredictable than patents directed towards the mechanical arts.⁴¹ This difference makes it harder to apply the obvious-to-try standard set forth in *KSR* to the more complex pharmaceutical cases. For instance, the standard set forth in *KSR* holds that if a known problem existed at the time of the invention and the invention encompasses an obvious solution to that problem, then it is non-patentable. While this standard may be readily applicable to a patent for a mechanical device, it is not as readily applicable to a pharmaceutical patent. As a result, the Federal Circuit has been cautious in how it applies *KSR* in these types of cases.⁴²

III. PHARMACEUTICAL CASES POST-*KSR*: *PFIZER V. APOTEX*

¶17 The uncertainty caused by the ruling in *KSR* in regards to pharmaceutical patent cases is exemplified by the Federal Circuit’s ruling in *Pfizer v. Apotex*.⁴³ The decision in *Pfizer* was the Federal Circuit’s first obviousness case following *KSR*, and it starkly contrasts with the decision recently issued by the Federal Circuit in *Unigene v. Apotex*.⁴⁴

¶18 In *Pfizer*, Pfizer Inc. obtained a patent for the drug Norvasc®, which contains amlodipine besylate.⁴⁵ Prior to the use of this patent, Pfizer had invented amlodipine (a dihydropyridine) and discovered its anti-hypertensive and anti-ischemic pharmacological properties.⁴⁶ It had obtained a U.S. patent for “certain dihydropyridine compounds and their pharmaceutically-acceptable acid addition salts.”⁴⁷ This previously issued patent stated “that the pharmaceutically-acceptable acid addition salts of amlodipine ‘are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulphate, phosphate or acid

³⁹ *Id.*

⁴⁰ *Id.* at 402–03.

⁴¹ Katherine M.L. Hayes, *Three Years Post-KSR: A Practitioner’s Guide to “Winning” Arguments on Obviousness and a Look at What May Lay Ahead*, 9 NW. J. TECH. & INTELL. PROP. 243, 253 (2010).

⁴² *Id.* at 243.

⁴³ *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

⁴⁴ *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1355 (Fed. Cir. 2011), *cert. denied*, 132 S.Ct. 1755 (2012).

⁴⁵ *Pfizer*, 480 F.3d at 1353.

⁴⁶ *Id.*

⁴⁷ *Id.*

phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts,⁴⁷ and the preferred salt is maleate.”⁴⁸ This patent did not mention the use of besylate as an acceptable anion. Because of issues with chemical instability and stickiness of the tablet blend when maleate was the anion that was used, Pfizer developed the amlodipine besylate formulation and obtained a patent for this formulation.⁴⁹

¶19 Before the expiration of Pfizer’s patent, Apotex filed an Abbreviated New Drug Application (ANDA) with the U.S. Food and Drug Administration (FDA) seeking approval to commercially sell amlodipine besylate tablets.⁵⁰ As a result, Pfizer filed a patent infringement action against Apotex, and Apotex counterclaimed that Pfizer’s patent was invalid due to obviousness.⁵¹ Although the district court rejected Apotex’s claim that the patent was invalid due to obviousness,⁵² the Federal Circuit reversed, determining that the patent claims were obvious in light of the prior art and therefore invalid.⁵³

¶20 In making this determination, the Federal Circuit noted that one of ordinary skill in the art would have been motivated to combine the prior art references to produce the amlodipine besylate of the claims.⁵⁴ Pfizer argued that the use of besylate in the formulation would not have been obvious, as the prior art reference that mentioned the use of besylate stated that it was “one of the most rarely used anions in the pharmaceutical industry, as only 0.25% of approved drugs . . . were besylate salts.”⁵⁵ The Federal Circuit was not persuaded by this argument.

¶21 First, the Federal Circuit noted that a skilled chemist at the time would have the ability to make salts of acceptable quality in the industry by using known ingredients.⁵⁶ As “the genus of FDA-approved anions at the time was small,” the fact that besylate was used as an anion only 0.25% of the time was not highly probative or dispositive.⁵⁷ The court seemingly ignored the fact that besylate was not a commonly used anion and concluded that the fact that it was listed as an FDA-approved anion would make it reasonable for one of ordinary skill in the art to use to develop the amlodipine besylate formulation of Pfizer’s patent.

¶22 In addition, the Federal Circuit noted the favorable qualities of besylate, such as acid strength and solubility, in determining obviousness.⁵⁸ The court acknowledged that none of the prior art references that suggested the use of besylate salt in the pharmaceutical described the pharmaceutical for treating hypertension or angina, which is what Pfizer’s drug was used to treat.⁵⁹ However, the court ruled that this was unimportant because the besylate portion of the acid addition salt has no therapeutic effect, and instead functions as a means of delivering the amlodipine part of the molecule

⁴⁸ *Id.*

⁴⁹ *Id.* at 1353–54.

⁵⁰ *Id.* at 1352.

⁵¹ *Id.*

⁵² *Id.* at 1356.

⁵³ *Id.* at 1358–59.

⁵⁴ *Id.* at 1364.

⁵⁵ *Id.* at 1362.

⁵⁶ *d.*

⁵⁷ *Id.* at 1363.

⁵⁸ *d.*

⁵⁹ *Id.*

to the body.⁶⁰ Therefore, the Federal Circuit reasoned that because besylate had the favorable characteristics listed above, a person of ordinary skill in the art would have been motivated to choose besylate as the anion in the salt.⁶¹

¶23 This reasoning by the Federal Circuit appears to indicate that pharmaceutical patents are affected by the decision in *KSR* and therefore may be more susceptible to findings of obviousness that were not found under the TSM standard that was routinely applied by the Federal Circuit before *KSR*.⁶² The Court in *KSR* had ruled that if “there is a design need or market pressure to solve a problem and there is a finite number of identified, predictable solutions, a person of ordinary skill in the art has reason to pursue the known options within his or her technical grasp.”⁶³ Therefore, the implementation of these solutions is the product of ordinary skill and common sense, not innovation.⁶⁴ Further, in *KSR* the Court ruled that although the TSM test still has value, it should not be applied too strictly. The Court noted that if a known problem existed at the time of the invention, and the patent’s claims encompass an obvious solution, then the patent fails to satisfy § 103’s nonobviousness requirement.⁶⁵

¶24 In this case, there was a design need and a known problem, as Pfizer’s old formulation that used maleate instead of besylate had chemical instability problems and tablet sticking problems.⁶⁶ The Federal Circuit, in applying the teaching of *KSR*, therefore seemingly disregarded the rarity of using besylate as the anion in the salt formulation. The court instead reasoned that because there existed a known problem with the maleate and a design need to work around it as the anion used in the formulation, the fact that besylate is listed as a potential anion in the prior art would be enough to lead someone of ordinary skill in the art to use it in formulating the pharmaceutical. As will be discussed later in Part IV, this reasoning starkly contrasts with the Federal Circuit’s subsequent reasoning in *Unigene*.

¶25 In addition to looking at the motivation to combine, the Federal Circuit looked at the *Graham* factor of secondary considerations and ruled that the patent claims were obvious. Pfizer had argued the use of besylate in the formulation yielded unexpected results and provided a pharmaceutical composition that was “sufficiently nonsticky to obtain commercial processability,” which indicated the pharmaceutical was not an obvious formulation.⁶⁷ The Federal Circuit noted that although evidence of unexpected results can be used to rebut a *prima facie* case of obviousness,⁶⁸ “this secondary consideration does not overcome the strong showing of obviousness in the case.”⁶⁹

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² See Scott D. Locke & William D. Schmidt, *Protecting Pharmaceutical Inventions in a KSR World*, 50 IDEA 1, 21 (2009) (“The trend since the *KSR* decision appears that, at least initially, claims for enhancing bioavailability by processing techniques or changing how the pharmaceutical is taken would be viewed as obvious particularly if they utilize known techniques or methods to administer the pharmaceutical.”).

⁶³ *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007).

⁶⁴ *Id.* at 402–03.

⁶⁵ *Id.* at 419–20.

⁶⁶ *Pfizer*, 480 F.3d at 1353–54.

⁶⁷ *Id.* at 1370 (internal quotation omitted).

⁶⁸ *Id.* at 1369 (citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

⁶⁹ *Id.* at 1372.

Furthermore, the court noted that there is no evidence that the results were unexpected, as Pfizer failed to provide “any evidence of what the skilled artisan would have expected.”⁷⁰ The Federal Circuit reasoned that, since besylate was listed as one possible anion in the prior art, it would be expected that some of the anions listed in the prior art would have superior properties and some would have inferior properties; therefore, the successful use of besylate would not be an unexpected result.⁷¹

¶26 This consideration of secondary factors and resulting conclusion of obviousness aligns with a strict reading of *KSR*. In *KSR*, the Court ruled that “the combination of familiar elements . . . is . . . obvious when it does no more than yield predictable results.”⁷² In this case, the Federal Circuit ruled that the successful use of besylate would not be unexpected simply because it is one of the listed anions that has been used in pharmaceutical formulations and, according to the Court, it would be expected that some of those anions would have superior properties.⁷³ The Federal Circuit’s determination of what would qualify as expected results in *Pfizer* again stands in stark contrast with its ruling in *Unigene*, as will be discussed in Part IV.

¶27 After *Pfizer*, some courts continued to apply this stricter standard in pharmaceutical cases. For example, in *McNeil-PPC v. Perrigo*, the district court ruled the patent was obvious, even in light of unexpected results and commercial success with the patent.⁷⁴ However, the Federal Circuit, along with other courts, did not follow this stricter standard of *Pfizer*. For example, in *Takeda Chemical Industries v. Alphapharm*, the court found the patent nonobvious by applying a pre-*KSR* test for obviousness: the lead compound analysis.⁷⁵ The court ruled that even though the prior art taught the compound at issue, since the art taught away from using this compound and suggested that other compounds would be more successful, the patent was valid.⁷⁶ The court distinguished its ruling from *Pfizer* by saying the prior art in this case required choosing from over ninety different compounds, whereas in *Pfizer* it only involved fifty-three pharmaceutically-acceptable anions narrowed down to a few, including the one chosen to be used in the patent.⁷⁷

IV. ANALYSIS OF *UNIGENE V. APOTEX*

¶28 After the decision in *Pfizer*, uncertainty remained regarding nonobviousness in pharmaceutical patents. In August 2011, the Federal Circuit appeared to set forth an enhanced standard for addressing obviousness in pharmaceutical patents in its decision in *Unigene v. Apotex*.

¶29 In *Unigene*, the Federal Circuit held that the patent claims at issue were not obvious in light of the prior art.⁷⁸ Unigene Laboratories, Inc., owns the patent for the drug

⁷⁰ *Id.* at 1371 (emphasis omitted).

⁷¹ *Id.*

⁷² *KSR*, 550 U.S. at 416.

⁷³ *Pfizer*, 480 F.3d at 1371.

⁷⁴ 516 F. Supp. 2d 238, 255 (S.D.N.Y. 2007).

⁷⁵ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

⁷⁶ *Id.* at 1359.

⁷⁷ *Id.* at 1359–60.

⁷⁸ *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1355 (Fed. Cir. 2011), *cert. denied*, 132 S.Ct. 1755 (2012).

Fortical[®], a nasal spray with the active ingredient salmon calcitonin.⁷⁹ Unigene filed a New Drug Application (NDA) for Fortical[®] and claimed Miacalcin[®], a drug marketed by Novartis International AG, as its reference drug.⁸⁰ Both of these drugs use salmon calcitonin as their active ingredient, but each has a different formulation.⁸¹ The important formulation difference is that Miacalcin[®] uses benzalkonium chloride (BZK) as a preservative, absorption enhancer, and surfactant, whereas Fortical[®] uses 20 mM of citric acid as an absorption enhancer and stabilizer/buffer, polyoxyethylene(2) sorbitan monooleate (polysorbate 80) as a surfactant, and phenylethyl alcohol and benzyl alcohol as preservatives.⁸²

¶30 The issue arose when Apotex filed an ANDA with the FDA to sell a generic version of Fortical[®] before Unigene's patent expired.⁸³ Unigene filed an infringement action against Apotex, and Apotex alleged there was no infringement due to patent invalidity under § 103.⁸⁴ The District Court for the Southern District of New York ruled that “no prior art teaches the use of 20 mM citric acid to achieve ‘both shelf stability and enhanced bioavailability’ in a nasal salmon calcitonin formulation” and that it would not have been obvious to one having ordinary skill in the art to develop the formulation in the patent claim.⁸⁵

¶31 Affirming the district court's ruling, the Federal Circuit restated the standard set forth in *KSR*: that obviousness requires the showing that a person of ordinary skill in the art would have selected and combined the prior art references during the normal course of research and development to yield the claimed invention.⁸⁶ However, the Federal Circuit further noted “when design need and market pressure may dictate a commonsensical path using a finite number of identified predictable solutions to one of ordinary skill, deviations from that path are likely products of innovation.”⁸⁷

¶32 One of the main focuses of the Federal Circuit in determining nonobviousness was the inclusion of 20 mM of citric acid in the patent claim. The Federal Circuit not only focused on the concentration of citric acid that was claimed, it also focused on the functionality of the citric acid as an absorption enhancer and stabilizer/buffer, even though functionality was not explicitly laid out in the claim language.

¶33 Apotex argued that this claim was obvious in light of the reference drug Miacalcin[®] and other prior art references.⁸⁸ One prior art reference that Apotex cited was U.S. Patent No. 5,912,014 (filed Mar. 15, 1996) ('014 patent).⁸⁹ The '014 patent claimed a solid oral dosage of salmon calcitonin that uses citric acid, but at much higher concentrations than

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ *Id.* at 1355–56.

⁸² *Id.* at 1356.

⁸³ *Id.*

⁸⁴ *Id.*

⁸⁵ *Id.* at 1358.

⁸⁶ *See id.* at 1360 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)); *see also* *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009) (Newman, J., dissenting) (“The statutory criterion is whether the invention would have been obvious to persons of ordinary skill at the time of the invention, not whether it is sufficiently simple to appear obvious to judges after the discovery is finally made . . .”).

⁸⁷ *Unigene*, 655 F.3d at 1361.

⁸⁸ *Id.* at 1362.

⁸⁹ *Id.*

the 20 mM claimed.⁹⁰ Further, the '014 patent examined using citric acid for bioavailability, but it was examined in the context of a liquid injection into a rat duodenum and not for human use in liquid pharmaceutical formulations.⁹¹ The Federal Circuit reasoned that because the concentration of citric acid in the '014 patent was much higher than the 20 mM in the claim, and the use of citric acid for bioavailability was not in the liquid pharmaceutical formulation context, a person of ordinary skill in the art would not have used 20 mM of citric acid in place of the BZK in Miacalcin[®] during the normal course of research and development.⁹²

¶34 Furthermore, the Federal Circuit noted that even though another prior art reference (U.S. Patent No. 5,124,315 (filed June 17, 1991) ('315 patent)) teaches the use of 20.5 mM of citric acid in a liquid nasal salmon calcitonin formulation, since the patent clearly states the citric acid was not used as an absorption enhancing agent, but instead was only used as the acidic component of the buffer, one of ordinary skill in the art would not use this citric acid as a BZK substitute.⁹³ In its reasoning, the Federal Circuit therefore imparts functionality into the claims when it is not explicitly stated and uses this functionality to determine nonobviousness. Although the concentration of citric acid used in the liquid nasal salmon calcitonin formulation of the '315 patent is about 20 mM, as claimed in Unigene's patent, the Federal Circuit emphasized the fact that the citric acid in this prior art was used only as a buffer, not as an absorption enhancing agent as it was in Unigene's formulation.

¶35 Finally, the Federal Circuit also rejected obviousness claims based on the prior art reference of U.S. Patent No. 4,476,116 (filed Dec. 10, 1982) ('116 patent), which was directed towards nasal compositions with enhanced peptide absorption.⁹⁴ In the '116 patent, citric acid is listed as a potential absorption agent.⁹⁵ However, the Federal Circuit found that one of ordinary skill in the art would not have used citric acid as an absorption agent based on this reference because citric acid is one of over fifty options listed in the patent.⁹⁶ Furthermore, the Federal Circuit reasoned that since the '315 patent mentioned the absorption agent options of the '116 patent but stated they yielded discouraging results, one of ordinary skill in the art would not have considered 20 mM of citric acid as a suitable absorption agent in the liquid nasal formulation of salmon calcitonin.⁹⁷

¶36 The Federal Circuit's decision in *Unigene* represents a departure from its earlier reasoning in *Pfizer*. In *Pfizer*, the court found that replacing maleate as the anion in the formulation with besylate was obvious in light of the prior art references, even though the prior art stated that besylate was only used 0.25% of the time in pharmaceutical formulations.⁹⁸ However, in *Unigene*, the Federal Circuit did not find it was obvious to use citric acid as an absorption enhancer, even though it was listed as such in the prior art reference to the '116 patent.⁹⁹ In this case, the Federal Circuit refused to find

⁹⁰ *Id.* at 1363.

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Id.*

⁹⁶ *Id.* at 1364.

⁹⁷ *Id.* at 1363.

⁹⁸ KSR, 480 F.3d at 1362–63 (Fed. Cir. 2007).

⁹⁹ *Unigene*, 655 F.3d at 1363.

obviousness because citric acid was one of fifty potential absorption enhancers listed in the prior art.¹⁰⁰ The court noted that not only was citric acid one of many potential absorption enhancers listed, it also yielded discouraging test results during experimentation.¹⁰¹ As a result, the Federal Circuit in this case refused to find that one of ordinary skill in the art would have used citric acid in the formulation as an absorption enhancer.

¶37 The Federal Circuit demonstrated differing analytical approaches in *Pfizer* and *Unigene*: in *Pfizer*, the court focused on the presence of a component to find obviousness, whereas in *Unigene*, the court determined that mere presence was insufficient to show obviousness. Consequently, the *Unigene* approach appears to be a departure from the strict reading of the ruling in *KSR* applied by the Federal Circuit in *Pfizer*. In *KSR*, the Court stated that if, at the time of the invention, a known problem existed and the patent claims encompassed an obvious solution, then the patent can be proven obvious.¹⁰² The Court in *KSR* further noted that “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton,”¹⁰³ and therefore, the fact that prior art was not designed to solve the particular problem of the patent does not preclude it from being used to prove obviousness.¹⁰⁴ The *Unigene* court appears to revert towards a stricter TSM test and away from the ruling in *KSR*.

¶38 Additionally, in *Pfizer*, the Federal Circuit looked at whether the use of besylate instead of maleate would produce unexpected results that would render the claim nonobvious. The court determined that because besylate was listed in the prior art as one potential anion that can be used in that type of salt formulation, there were no unexpected results. Therefore, the claim was obvious. The court did not look closely at the functionality of the besylate and maleate to determine if the substitution would be nonobvious. On the other hand, in *Unigene*, the Federal Circuit paid close attention to the functionality of the components and determined that the patent claims were nonobvious because of the function the citric acid performed within the formulation.

¶39 This focus on functionality is particularly interesting because functionality was not part of *Unigene*’s claim language. The claim itself listed the components of the pharmaceutical formulation and the concentrations of each component within the formulation. However, nowhere in the claim was there a mention of the functionality of each component. Instead, it appears that the Federal Circuit read functional language into the claims from the specification, and then used this as evidence to determine that the prior art did not render the claims obvious. This reasoning constitutes a definite departure from the reasoning applied in *Pfizer*.¹⁰⁵

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007).

¹⁰³ *Id.* at 421.

¹⁰⁴ *Id.*

¹⁰⁵ See *Unigene v. Apotex: Federal Circuit Discusses Standard for Prima Facie Obviousness of Pharmaceutical Composition Claims Post-KSR*, WILSON SONSINI GOODRICH & ROSATI (Sept. 2011), <http://www.wsgr.com/publications/PDFSearch/wsgralert-unigene-v-apotex.pdf>.

V. IMPLICATIONS OF *UNIGENE V. APOTEX* ON THE FUTURE OF PHARMACEUTICAL PATENTS

¶40 *Unigene* appears to set forth an enhanced standard for determining obviousness in pharmaceutical patent claims. The court in *Pfizer* did not address the intricacies of designing pharmaceutical formulations and instead solely focused on whether components of the pharmaceutical formulation were mentioned in the prior art. However, in *Unigene*, the court looked beyond whether the components were mentioned in the prior art and focused on the functionality of the components. While *Unigene* did not expressly overrule the decision in *Pfizer*, it appears that the Federal Circuit now recognizes the inherent complexities and challenges involved in pharmaceutical patents and has articulated a standard that appropriately addresses these challenges.

¶41 For example, in both *Pfizer* and *Unigene*, the patent claims at issue were for pharmaceutical formulations that were each derived from chemically similar drugs that were known in the prior art.¹⁰⁶ Each of these cases illustrates how even small chemical differences in the structure and chemical makeup of a pharmaceutical formulation can have therapeutic implications.¹⁰⁷ Because of the potential therapeutic advantages that could arise from modifying chemically similar drugs, the FDA Center for Drug Evaluation and Research awards these “chemically similar pharmaceutical candidates expedited review status,”¹⁰⁸ incentivizing the research and development of these drugs.¹⁰⁹

¶42 As seen in *Pfizer*, however, patents directed towards chemically similar drugs that have substantial structural similarity to the previously known compound can lead to a rejection for obviousness.¹¹⁰ The problem with this rejection under obviousness is that pharmaceutical companies are not as likely to invest in research and development to produce new drugs if they feel that the drugs will not be eligible for patent protection.¹¹¹ Therefore, the need to remove patents that are truly obvious and non-innovative from the market must be balanced against the need to avoid a prohibitively high standard in the patent process that may stunt scientific research and development.

¶43 One further problem with the ruling in *Pfizer* was the Federal Circuit’s implicit application of the “obvious to try” standard to reject the claims as obvious. Briefly, the

¹⁰⁶ See 655 F.3d at 1355–56 (Fortical® was derived from the reference drug Miacacilin® but replaced the BZK of Miacacilin® with citric acid, polysorbate 80, phenylethyl alcohol and benzyl alcohol. The patentable feature was found to be the concentration of citric acid claimed); 480 F.3d at 1353 (explaining that Norvasc® was an amlodipine besylate drug that was a modification of the patented amlodipine drugs. The patentable feature Pfizer tried to claim was the replacement of maleate as the preferred anion with besylate).

¹⁰⁷ See *Changing Patterns of Pharmaceutical Innovation*, NAT’L INST. FOR HEALTH CARE MGMT. FOUND. 4–10 (2002), <http://www.nihcm.org/pdf/innovations.pdf>. In addition to approving new molecular entities (i.e. medicines containing active ingredients that have never before been approved for the U.S. market), the U.S. Food and Drug Administration (FDA) also approves new products whose active ingredients are chemical derivatives of previously approved drugs, which may be safer or more effective than the original medication.

¹⁰⁸ Andrew V. Trask, “*Obvious to Try*”: A Proper Patentability Standard in the Pharmaceutical Arts?, 76 *FORDHAM L. REV.* 2625, 2627 (2008).

¹⁰⁹ *Id.*

¹¹⁰ See 480 F.3d at 1363–64; see also MPEP § 2144.09 (8th ed. Rev. 6, Sept. 2007) (“A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.”).

¹¹¹ See BERNICE SCHACTER, *THE NEW MEDICINES: HOW DRUGS ARE CREATED, APPROVED, MARKETED AND SOLD* 52 (2006); see also C. MERLE CRAWFORD, *DEFINING THE CHARTER FOR PRODUCT INNOVATION IN GENERATING TECHNOLOGICAL INNOVATION* 163, 175 (Edward B. Roberts ed., 1987).

obvious to try test as applied in the pharmaceutical industry focused on whether it would have been obvious to chemically modify a prior art pharmaceutical compound to arrive at the claimed compound.¹¹² However, this standard tends to discount whether a person of ordinary skill in the art would have possessed any “reasonable expectation of success” when modifying the compound.¹¹³ In *Pfizer*, although there was no indication in the prior art that besylate salt of amlodipine was anything but merely obvious to try, the Federal Circuit still ruled that it would not only have been obvious to try, but also obvious to make.¹¹⁴ This seemingly disregarded the prior art that stated that the use of besylate as an anion in pharmaceutical formulations was rare,¹¹⁵ as well as the undisputed testimony that the advantageous properties of amlodipine besylate could not have been predicted.¹¹⁶

¶44 The danger of this obvious to try standard is that it might hamper future pharmaceutical research by removing an incentive for researchers to develop new pharmaceutical drugs. There are high costs associated with pharmaceutical research, and if researchers feel they will not obtain patent protection, then there will be no impetus to pursue that particular research.¹¹⁷ Also, an easier invalidation process due to obviousness might make it more difficult to exclude generics from the market.¹¹⁸ Because the pharmaceutical industry is dependent upon patent protection to exclude generic competitors from the market,¹¹⁹ this could have negative ramifications for the pharmaceutical industry.

¶45 The approach the Federal Circuit took in *Unigene* is more beneficial to the pharmaceutical industry as a whole precisely because of the dangers of the strict standard applied in *Pfizer*. In *Unigene*, the court did not apply an obvious to try standard and instead implemented a stricter standard in determining obviousness by requiring the functionality of the components in the prior art to match up to the functionality of the component in the patent claim.¹²⁰

¶46 If the Federal Circuit in *Unigene* had approached the prior art and the patent claim as it had in *Pfizer*, it most likely would have found the claim to be obvious based on the prior art of record, since the prior art mentioned using citric acid in a salmon calcitonin liquid nasal formulation—the patent claim—and it taught using this citric acid in a

¹¹² Trask, *supra* note 109, at 2634.

¹¹³ *Id.* (“Professor Robert P. Merges asserts that ‘obvious to try’ is a subset of ‘the reasonable expectation of success standard.’ . . . In the context of research involving methodical screening, Merges explains that where a researcher is presented with a large number of variables and where the prior art provides insufficient guidance to reduce the variables to a ‘manageable level,’ then the researcher cannot be reasonably certain of success. . . . A finding of obviousness despite the lack of a reasonable expectation of success constitutes application of the ‘obvious to try’ standard.”) (quoting Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 HIGH TECH. L.J. 1, 40–42 (1992)).

¹¹⁴ 480 F.3d at 1366.

¹¹⁵ *Cf. id.* at 1362 (noting the prior art stated that besylate was one of most rarely used anions in pharmaceutical formulations, as it is used only 0.25% of the time).

¹¹⁶ *See id.* at 1356–57.

¹¹⁷ SCHACTER, *supra* note 112.

¹¹⁸ Rebecca S. Eisenberg, *Pharma’s Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 377 (2008).

¹¹⁹ *Id.*

¹²⁰ *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360–62 (Fed. Cir. 2011), *cert. denied*, 132 S.Ct. 1755 (2012) (looking at the functionality of citric acid in the patent claim as an absorption enhancer and failed to find the mention of citric acid in pharmaceutical formulations in the prior art as indicative of obviousness. The court instead focused on the prior art language that stated citric acid as an absorption enhancer yielded discouraging results).

similar concentration to that which was claimed. However, the Federal Circuit in *Unigene* instead focused heavily on the fact that the prior art that mentioned using citric acid in about the same concentration as that used in the patent claims neglected to teach that it was used as an absorption enhancer.¹²¹

¶47 This focus on functionality was not seen in *Pfizer* and is even more interesting given that the functionality of the components is not part of the claim language itself. In the examination of patents to determine obviousness, it is the claim language that is important and the determinative factor of what will be actually patented.¹²² Furthermore, although the specification is relevant as it might provide explanation for claims, the actual patented subject matter is that which is set forth in the claim language, not the specification.¹²³ Therefore, when the Federal Circuit in *Unigene* ruled that the patented claim was valid despite the prior art teaching the use of citric acid in a similar concentration to that in the patented claim, it was imparting limitations from the specification into the claim language. The Federal Circuit reasoned that because the prior art failed to teach that citric acid could function as an absorption enhancer, it was not relevant to the obviousness inquiry. This analytical shift by the Federal Circuit to impart limitations from the specification into the claim language could have interesting repercussions on the field of patent law, especially if applied to other industries.

¶48 By imparting functionality that is listed in the specification into the claim language itself, the Federal Circuit goes against the interpretation of claim language that is set forth in the Manual of Patent Examining Procedure (MPEP)¹²⁴ of the United States Patent and Trademark Office (USPTO). According to the MPEP, claims are to be “given their broadest reasonable interpretation consistent with the specification.”¹²⁵ However, the reading of limitations from the specification into the claim is found to be an impermissible importation of subject matter from the specification into the claim.¹²⁶ Therefore, the imparting of functionality into the claim language could be argued to be in opposition to the standards set forth by the MPEP.

¶49 Although imparting functionality may be a necessary approach to use in the field of pharmaceutical patents due to their inherent complexity, this same approach should not be applied in other fields (i.e. mechanical arts). Such an approach would result in an overly limiting model that would render it more difficult to find patents obvious in the mechanical arts, even when they should be found obvious. The requirement that functionality align in both the prior art and the patent at issue in the mechanical field is not as necessary as requiring the same alignment in the pharmaceutical industry because mechanical patents do not face the same design challenges as pharmaceutical patents.

¶50 Another reason that the enhanced standard set forth in *Unigene* is useful in the pharmaceutical patent context is that it might make it harder to invalidate pharmaceutical

¹²¹ *Id.* at 1363.

¹²² See MPEP § 2111 (8th ed. Rev. 6, Sept. 2007) (“During patent examination, the pending claims must be ‘given their broadest reasonable interpretation consistent with the specification.’”).

¹²³ See *id.* § 2111.01 (“Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.”).

¹²⁴ The MPEP is the standard used by examiners when determining whether or not a patent should be granted.

¹²⁵ MPEP, *supra* note 124 § 2111.

¹²⁶ See *id.* (Claim Interpretation; Broadest Reasonable Interpretation).

patents for obviousness. This is particularly relevant in the pharmaceutical context because industries that work toward developing new drugs have a great need for patent protection.¹²⁷ One reason for this is the great cost associated with research and development of a new pharmaceutical.¹²⁸ Also, the FDA requires a long and rigorous set of tests for companies to pass before they can release a pharmaceutical into the market.¹²⁹ Because of this, pharmaceutical research is an inherently uncertain discipline.¹³⁰

¶51 As proposed by Professor Merges, obviousness should be viewed as a function of uncertainty, and when uncertainty is high, the courts should moderately lower the standard of patentability to compensate for the risk of failure.¹³¹ The enhanced standard set forth in *Unigene*, which makes it more difficult to invalidate a patent based on obviousness, seems to provide this lower standard of patentability that compensates for the uncertainty of pharmaceuticals.

¶52 On the other hand, it can be argued that this sliding scale method of compensating for uncertainty suffers from defects, because it establishes a standard that differs from industry to industry. Other industries, aside from the pharmaceutical industry, also have high uncertainty and arguably should be given more leeway in standards for obviousness. This issue is just one of many challenges patent litigators and courts will likely face in the future as post-*KSR* standards for obviousness and industry-specific standards are challenged.

¶53 In regards to the pharmaceutical industry, the court's recognition in *Unigene* of the high uncertainty involved in pharmaceutical patents should result in a lower standard for patentability. This will facilitate the process for pharmaceutical companies to obtain patent protection for their products. As noted above, this standard could have a negative impact, as it might result in a greater bar to generics entering the market. However, the positive results for society—namely, strengthened incentives for pharmaceutical research and development—seem to outweigh these negatives. Because the cost of research and development in the pharmaceutical area is so great, a company that is more likely to obtain patent protection will be more likely to invest time and resources into developing new drugs. This will drive innovation in the pharmaceutical arena and provides society with beneficial new treatments.

VI. CONCLUSION

¶54 The enhanced standard set forth in *Unigene v. Apotex* for determining obviousness in pharmaceutical formulations was a step in the right direction for the Federal Circuit. The previous standard established in *KSR* created uncertainty in determining obviousness in the world of pharmaceutical patents that was problematic for the industry as a whole,

¹²⁷ Yi-Chen Su, *What About Know-How: Heightened Obviousness and Lowered Disclosure is Not a Panacea to the American Patent System for Biotechnology Medication and Pharmaceutical Inventions in the Post-KSR Era*, 14 MARQ. INTELL. PROP. L. REV. 321, 329 (2010).

¹²⁸ Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1581 (2003) (“In the pharmaceutical industry . . . the [research and development], drug design, and testing of a new drug can take a decade or more and cost, on average, hundreds of millions of dollars.”).

¹²⁹ *Id.* at 1616.

¹³⁰ *See, e.g., Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1208–09 (Fed. Cir. 1991) (finding that biotechnology is an uncertain discipline).

¹³¹ Trask, *supra* note 109.

as patents are incredibly important to the innovation of new drugs. The decision in *Pfizer*, reached shortly after *KSR*, exemplified the uncertainty left by the Supreme Court in determining obviousness in pharmaceutical patent cases. The court in *Pfizer* applied a strict reading of *KSR* to the pharmaceutical patent in question to find it obvious, leaving doubt in the minds of pharmaceutical researchers as to whether obtaining patent protection for their new pharmaceutical products would be problematic. The Federal Circuit did not set forth a clear obviousness standard until the most recent decision in *Unigene*.

¶55 *Unigene* not only sets forth an enhanced standard, it also appears to make it more difficult to invalidate pharmaceutical patents as obvious. Focusing the inquiry on the functionality of the components in the prior art relative to the functionality of the components in the patent adds an extra protection against a finding of obviousness for pharmaceutical patents. Furthermore, the court in *Unigene*, unlike the court in *Pfizer*, considered experimentation results by finding nonobviousness when there would be unexpected results generated by the use of a particular compound. Thus, the resulting standard established in *Unigene* improves upon the previous standard because it both enhances the clarity of the test and provides appropriate protection for research and development within the pharmaceutical industry. Moving forward, the Federal Circuit and the lower courts should continue to apply this enhanced standard and not be as quick to render pharmaceutical formulation claims non-obvious.