"OBVIOUS TO TRY": A PROPER PATENTABILITY STANDARD IN THE PHARMACEUTICAL ARTS?

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Pharmaceutical research often entails making small modifications to candidate drug molecules—modifications that might be deemed "obvious to try"—and then studying the largely unpredictable, yet critical, resulting biological effects. Recognizing this characteristic unpredictability, the U.S. Court of Appeals for the Federal Circuit has traditionally upheld the patentability of obvious-to-try pharmaceutical inventions. This approach has been challenged, however, by the U.S. Supreme Court's 2007 decision in KSR International Co. v. Teleflex Inc. *This Note reviews the history of the obvious-to-try test and considers the Federal Circuit's post-*KSR *inconsistency regarding obviousness in the pharmaceutical arts. This Note argues that* KSR *does not permit courts to deny the patentability of a pharmaceutical invention simply because it would have been obvious to try.*

INTRODUCTION

Small chemical differences can lead to unexpectedly drastic therapeutic implications. Perhaps the most alarming illustration involves thalidomide, a sedative drug marketed to pregnant women that, prior to its removal from the market, caused physical malformations in as many as 12,000 newborns.[1] The active ingredient in thalidomide consists of a pair of molecules that are chemically identical but for their overall spatial arrangement.[2] Underscoring the exceptional particularity with which the

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1. *See generally* William A. Silverman, *The Schizophrenic Career of a "Monster Drug,"* 110 Pediatrics 404 (2002). Thalidomide was marketed as a sedative drug outside the United States from 1957 to 1961 as a safe alternative to barbiturates. *See id.* at 405–06. In particular, thalidomide was advertised as "'the drug of choice' for pregnant women with morning sickness and nausea." *Id.* at 405. When physicians recognized the teratogenicity of thalidomide, the drug was removed from the market; however, it has been estimated that between 8000 and 12,000 infants were born with physical malformations as a result of thalidomide. *See id.* at 406.

2. The difference between thalidomide's two forms (chemically termed "enantiomers") is analogous to the difference between a person's left and right hands: both hands are

body recognizes chemical substances, studies indicate that one of these molecules is associated predominantly with causing birth defects, whereas the other is responsible for inducing sleep.[3] In theory, were it possible to treat a patient with only the molecule causing sedation, the thalidomide tragedy might have been altogether avoided.[4]

The thalidomide story demonstrates that nearly identical chemical substances may exhibit critically different biological effects, and therefore highlights the need for thorough and meticulous research to promote the development of safe, effective pharmaceuticals.[5] Beyond characterizing potentially toxic impurities, however, the investigation of pharmaceutical molecules that are chemically similar to drugs approved previously may also yield therapeutic candidates that provide significant clinical improvement in the diagnosis, treatment, or prevention of disease.[6]

identical in terms of their constituents (e.g., four fingers, one thumb, a forehand, and a backhand) and order of connectivity, but differ in terms of spatial arrangement (e.g., the thumbs point in opposite directions). *See generally* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stan. Tech. L. Rev. 2, ¶¶ 5–11, *available at* http://stlr.stanford.edu/pdf/darrow-patentability.pdf (discussing the chemistry of enantiomers and the patentability thereof).

3. *See* J. Blake Bartlett et al., *The Evolution of Thalidomide and its IMiD Derivatives as Anticancer Agents*, 4 Nature Reviews Cancer 1, 2 (2004); *see also* Tommy Eriksson et al., *Stereospecific Determination, Chiral Inversion In Vitro and Pharmacokinetics in Humans of the Enantiomers of Thalidomide*, 7 Chirality 44, 44–45 (1995).

4. *See* Bartlett et al., *supra* note 3, at 2. Adding a further layer of complexity, thalidomide undergoes "racemization" in the body, meaning that thalidomide interconverts between its two forms under physiological conditions, and thus will always present a risk of teratogenicity. *See id.*; *see also* Eriksson et al., *supra* note 3, at 51.

5. *See, e.g.*, *In re* Merck & Co., 800 F.2d 1091, 1101 (Fed. Cir. 1986) (Baldwin, J., dissenting) ("Congress gave pragmatic recognition to the difficulty of determining whether a new drug is useful by its enactment of the 1962 amendment to 21 U.S.C. § 321. That action was taken in response to problems caused by [the] tranquilizer[] thalidomide."). Thalidomide is but one example of how small structural changes to a pharmaceutical molecule may elicit large biological effects; another example is the epilepsy drug R-(–)-vigabatrin, which becomes highly toxic upon conversion to its mirror-image enantiomer. *See* Imran Ali et al., *Role of Racemization in Optically Active Drugs Development*, 19 Chirality 453, 454 (2007).

6. *See, e.g.*, Nat'l Inst. for Health Care Mgmt. Found., Changing Patterns of Pharmaceutical Innovation 4–10 (2002) [hereinafter NIHCM Report], *available at* http://www.nihcm.org/~nihcmor/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. *See id.* at 4–5. For example, in the period of 1989 to 2000, incrementally modified drugs (a category that includes chemical derivatives of previously approved pharmaceuticals) contributed more than new molecular entities to the observed increase in approved drugs offering clinical improvements. *See id.* at 7. *But see, e.g.*, Melody Petersen, *New Medicines Seldom Contain Anything New, Study Finds*, N.Y. Times, May 29, 2002, at C1 (construing NIHCM Report, *supra*, as evidence that pharmaceutical companies use "advertising to sell drugs that are essentially line extensions of existing medicines"); Rosanne Spector, *Me-Too Drugs: Sometimes They're Just the Same Old, Same Old*, Stan. Med. Mag., Summer 2005, at 16, 16, *available at* http://stanmed.stanford.edu/2005summer/drugs-metoo.html (contending that chemically similar drugs may not offer substantial improvements over their previously approved counterparts).

Recognizing these potential advantages, the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research awards such chemically similar pharmaceutical candidates expedited review status if they offer, for example, increased effectiveness, reduction of side effects, or evidence of safety and effectiveness for a new patient subpopulation.[7] Such cases[8] emphasize the significant therapeutic advantages that can arise from small chemical changes, and reinforce the rationale for incentivizing research into chemically similar pharmaceutical molecules.

Pharmaceutical candidates derived from chemically similar drugs may offer significant therapeutic advantages in the clinic,[9] but they face an uphill battle in the U.S. Patent and Trademark Office (PTO). Substantial structural similarity to a previously known compound can form the basis of an obviousness rejection,[10] although each case requires individualized evaluation on its own particular facts.[11] In attempting to interpret the recent pronouncement of the U.S. Supreme Court on legal obviousness,[12] several court decisions have diverged as to the correct application of the statutory nonobviousness requirement in cases involving chemical similarity in the pharmaceutical arts.[13] A key issue in such cases is whether an obviousness

7. *See, e.g.*, Ctr. for Drug Evaluation and Research, FDA, Manual of Policies and Procedures 6020.3, at 2 (2007), *available at* http://www.fda.gov/cder/mapp/6020.3R.pdf (outlining categories for which a submitted drug may be considered for expedited "priority" review); *see also* Ctr. for Drug Evaluation and Research, 2005 Report to the Nation: Improving Public Health Through Human Drugs 12–15 (2005), *available at* http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf (noting that priority review is possible for new drug applications whether or not they contain new molecular entities).

8. For example, in 2006, the FDA approved under expedited priority review a chemically modified version of the common analgesic ibuprofen for the treatment of a complication associated with a significant proportion of prematurely born infants. Specifically, the product is ibuprofen lysine, a pharmaceutical salt prepared by reacting ibuprofen with a biologically ubiquitous amino acid; the approved indication is "patent ductus arteriosus," the failure of an essential blood vessel to close properly after birth. *See* Grace Poon, *Ibuprofen Lysine (NeoProfen) for the Treatment of Patent Ductus Arteriosus*, 20 Baylor U. Med. Center Proc. 83, 83 (2007); FDA, CDER Priority Drug and Biologic Approvals in Calendar Year 2006, http://www.fda.gov/cder/rdmt/InternetPriority06.htm (last visited Feb. 20, 2008).

9. *See, e.g.*, *supra* note 8.

10. *See* U.S. Patent & Trademark Office, Manual of Patent Examining Procedure § 2144.09 (8th ed. 2007) [hereinafter MPEP] ("A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.").

11. *See, e.g.*, *In re* Dillon, 919 F.2d 688, 692–93 (Fed. Cir. 1990) (en banc) ("[S]tructural similarity between claimed and prior art subject matter . . . creates a *prima facie* case of obviousness . . . . [However,] [e]ach situation must be considered on its own facts . . . .").

12. *See generally* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007) (invalidating claims to an automobile accelerator pedal equipped with electronic sensor due to obviousness).

13. *Compare* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350, 1359–60 (Fed. Cir. 2007) (upholding claims to an antidiabetic compound despite an obviousness attack based on a structurally similar prior art compound), *and* Sanofi-Synthelabo v. Apotex Inc., 492 F. Supp. 2d 353, 388–92 (S.D.N.Y. 2007), *appeal docketed*, No. 2007-1438 (Fed. Cir. Sept. 4, 2007) (upholding claims to an antistroke compound despite an obviousness

holding may be properly based on a finding that it would have been obvious for a skilled researcher to try to make the claimed invention, regardless of whether the person would have possessed a reasonable expectation of success.[14]

As this Note demonstrates, the origins of the obvious-to-try test predate the statutory nonobviousness patentability requirement. However, beginning with the mandate of 35 U.S.C. § 103, that nonobviousness be adjudged objectively and by taking into account the invention "as a whole,"[15] staunch opposition to the obvious-to-try test eventually took hold in the U.S. Court of Customs and Patent Appeals (CCPA)[16] and its successor court, the U.S. Court of Appeals for the Federal Circuit. Nevertheless, in 2007, the Supreme Court upended the settled opposition to this patentability test in the landmark[17] case *KSR International Co. v. Teleflex Inc*.[18] Since then, courts have struggled to reconcile an ostensible adoption of the obvious-to-try test in *KSR*, which involved subject matter in the mechanical field, to inventions in the characteristically unpredictable pharmaceutical arts.[19]

This Note traces the history of the obvious-to-try test and analyzes its current status, particularly with respect to the pharmaceutical arts. Part I begins by introducing the significance of the nonobviousness patentability requirement in the pharmaceutical arts, including the function of the obvious-to-try test. Part I then examines the evolution of the obvious-to-try patentability standard up through the 2007 Supreme Court decision in *KSR*.[20] The analysis demonstrates that although a version of the obvious-

challenge over the prior art disclosure of a closely related chemical structure), *with* Pfizer, Inc. v. Apotex, Inc. 480 F.3d 1348, 1364–69 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007) (invalidating claims to an antihypertension compound as obvious over the prior art disclosure of, inter alia, an alternative chemical modification of a claimed compound).

14. *See Takeda*, 492 F.3d at 1359; *Pfizer*, 480 F.3d at 1365–66; *Sanofi*, 492 F. Supp. 2d at 391–92.

15. A patent may not be granted if the "subject matter as a whole" would have been obvious to "a person having ordinary skill in the art." *See* 35 U.S.C. § 103 (2000).

16. In 1982, the present-day U.S. Court of Appeals for the Federal Circuit, which has exclusive appellate jurisdiction over cases arising under the patent laws, succeeded the U.S. Court of Customs and Patent Appeals (CCPA). *See* 2 Donald S. Chisum, Chisum on Patents § 5.02[6], at 5-62 (2007).

17. "Though *KSR International Co. v. Teleflex, Inc.* is now widely acknowledged in the bar and the academy to be the most significant patent case in at least a quarter century, that view dramatically underestimates the importance of the decision." John F. Duffy, Commentary, KSR v. Teleflex*: Predictable Reform of Patent Substance and Procedure in the Judiciary*, 106 Mich. L. Rev. First Impressions 34, 34 (2007), http://www.michiganlawreview.org/firstimpressions/vol106/duffy.pdf; *see also* Linda Greenhouse, *High Court Puts Limits on Patents*, N.Y. Times, May 1, 2007, at C1 (referring to *KSR* as the U.S. Supreme Court's "most important patent ruling in years").

18. 127 S. Ct. 1727 (2007).

19. *See Takeda*, 492 F.3d 1350; *Pfizer*, 480 F.3d 1348; *see also infra* notes 186–88 and accompanying text (noting that the Federal Circuit denied Pfizer's petition for panel rehearing and rehearing en banc following *KSR*).

20. 127 S. Ct. 1727, 1734 (2007) (noting that the claimed invention involves a mechanism for combining an electronic sensor with an adjustable automobile pedal).

to-try test existed even before the statutory nonobviousness requirement, the enactment of 35 U.S.C. § 103 slowly but effectively signaled the end of "obvious to try" as a proper patentability standard.

Part II analyzes the inconsistent consequences of *KSR*'s discussion of "obvious to try" on the patentability of inventions in the pharmaceutical arts. In particular, this part contrasts the Federal Circuit's holdings in two pharmaceutical cases, *Pfizer, Inc. v. Apotex, Inc.*[21] and *Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*[22] In *Pfizer*, the court implicitly applied an obvious-to-try analysis to overturn a district court's finding of nonobviousness. In *Takeda*, on the other hand, the court rejected the argument that *KSR* endorsed the obvious-to-try test in the pharmaceutical arts. This part also discusses the PTO's initial interpretation of the *KSR* decision. Finally, this part introduces a third case, *Sanofi-Synthelabo v. Apotex Inc.*,[23] which is currently on appeal to the Federal Circuit and which may serve as a useful litmus test for indicating the court's view on the post-*KSR* obvious-to-try test.

Part III advocates a rejection of the *Pfizer* court's application of "obvious to try" for pharmaceutical inventions. This part proposes an interpretation of *KSR*'s obvious-to-try test that credits the context-specific nature of patent law, thereby aligning most closely with the *Takeda* court's view. The proposed approach emphasizes the irrelevance of the obvious-to-try test in the unpredictable pharmaceutical field. In doing so, the proposed approach encourages pharmaceutical and biomedical innovation in areas only dimly illuminated by the prior art—that is, "those efforts and attempts which go by the name of 'research.'"[24] As discussed in Part III, this interpretation would affirm the validity of the claimed invention at issue in the pending *Sanofi* appeal.

I. THE HISTORY AND SIGNIFICANCE OF THE OBVIOUS-TO-TRY TEST

A. *Obviousness and the Pharmaceutical Arts*

1. Pharmaceuticals and Intellectual Property Law

Like many industries in which the cost of development substantially exceeds the cost of product manufacture, intellectual property is a key component of the pharmaceutical industry.[25] The ability to obtain patent protection covering an approved drug product creates an incentive for pharmaceutical companies to make substantial preapproval investments in

21. 480 F.3d 1348 (Fed. Cir. 2007)
22. 492 F.3d 1350 (Fed. Cir. 2007).
23. 492 F. Supp. 2d 353 (S.D.N.Y. 2007).
24. *See In re* Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966).
25. *See, e.g.*, Philip W. Grubb, Patents for Chemicals, Pharmaceuticals and Biotechnology 230–44 (4th ed. 2004) (discussing the various types of pharmaceutical patent protection that may be obtained, including new chemical entities, pharmaceutical compositions, and pharmaceutical uses).

research and development,[26] including conducting expensive clinical trials and meeting stringent requirements for regulatory approval.[27] The same patent protection comes at a cost to consumers, however, by way of increased prices for innovative new medicines.[28] For this reason, Congress encouraged the growth of the generic pharmaceutical industry,[29] which provides low-cost versions of these innovative drugs at substantially reduced prices.[30] One key legislative provision favoring the growth of generics is the concept of "180-day exclusivity."[31] In essence, this provision awards six months of market exclusivity to the first generic company to challenge the validity of a patent covering a brand-name pharmaceutical product.[32] Challenges to patent validity thus represent a fulcrum balancing the twin aims of pharmaceutical innovation and affordable access to medicine.

26. *See, e.g.*, Biotech. Indus. Org. v. District of Columbia, 496 F.3d 1362, 1372 (Fed. Cir. 2007), *reh'g denied*, 505 F.3d 1343 (Fed. Cir. 2007) ("'We have long acknowledged the importance of the patent system in encouraging innovation. . . . Importantly, the patent system provides incentive to the innovative drug companies to continue costly development efforts.'" (quoting Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383 (Fed. Cir. 2006), *appeal docketed*, No. 2007-1438 (Fed. Cir. Sept. 4, 2007))).

27. Indeed, the cost of bringing a drug to market is large and apparently growing. In 1998, the pharmaceutical industry spent a total of $27 billion on research and development, and the FDA approved a total of twenty-four drugs. *See Beyond the Pill*, Economist, Oct. 27, 2007, at 76, 76. In 2006, by contrast, the industry spent $64 billion on research and development while the FDA approved only thirteen drugs. *Id.*

28. *See generally* FTC, Generic Drug Entry Prior to Patent Expiration: An FTC Study (2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf.

29. An important mechanism for encouraging the generic industry is the Drug Price Competition and Patent Term Restoration Act, known informally as the Hatch-Waxman Act, which, inter alia, provides an incentive for generic companies to challenge the validity of innovator companies' pharmaceutical patents. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360cc (2000) and 35 U.S.C. §§ 156, 271, 282 (2000)), *amended by* Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, tit. 11, 117 Stat. 2066, 2448–69 (current version at 21 U.S.C. § 355(j)(5)(C)(i) (2000) and 35 U.S.C. § 271(e)(5) (2000)).

30. "The robust generic drug industry owes its very existence to the [Hatch-Waxman] Act, and patent term extensions or restorations [as provided by the Act] are very important to the research-based pharmaceutical industry." Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 Food & Drug L.J. 187, 194 (1999); *see id.* at 193 (providing a "New Medicines Timeline" illustrating the temporal relationship between innovator and generic drug filing and approval).

31. *See generally* Erika King Lietzan, *A Brief History of 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, 59 Food & Drug L.J. 287 (2004) (chronicling the development of the Hatch-Waxman 180-day exclusivity provision and its substantial amendment in 2003).

32. The exclusivity provided is "against subsequent generic copies of the same innovator drug. This, it was thought, would encourage generic applicants." *Id.* at 288; *cf.* Colman B. Ragan, *Saving the Lives of Drugs: Why Procedural Amendments in Hatch-Waxman Litigation and Certification of* Markman *Hearings for Interlocutory Appeal Will Help Lower Drug Prices*, 13 Fed. Cir. B.J. 411, 413 (2004) ("This [180-day] exclusivity period can translate into a significant profit for the generic manufacturer to whom it is awarded and is the big prize that generic manufacturers fight over.").

At the heart of many patent validity challenges is the reality that not every innovation deserves a patent.[33] In determining whether a particular innovation merits patent protection, a court must assess whether the invention, at the time the patent application was filed, was new,[34] useful[35] and nonobvious.[36] Of these statutory patentability requirements, the most contentious is often the question of whether the claimed invention would have been obvious to a person of ordinary skill in light of the prior art.[37] The objective standard for an obviousness determination is found in 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.[38]

The Supreme Court's original reading of the statutory obviousness inquiry[39] remains today's principal governing interpretation.[40] *Graham v. John Deere Co.* held that obviousness is a question of law grounded in several factual determinations.[41] As described in the Supreme Court's

33. Indeed, Thomas Jefferson, who "might well be called the 'first administrator of our patent system,'" Graham v. John Deere Co., 383 U.S. 1, 7 (1966) (quoting P.J. Federico, *Operation of the Patent Act of 1790*, 18 J. Pat. Off. Soc'y 237, 238 (1936)), acknowledged "the difficulty of drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not." Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813), *in* 13 The Writings of Thomas Jefferson, 326, 335 (Andrew A. Lipscomb ed., Library ed. 1904); *cf.* 35 U.S.C. § 101 ("Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.").

34. *See* 35 U.S.C. § 102.

35. *See id.* § 101.

36. *See id.* § 103.

37. *See, e.g.*, Nonobviousness—The Ultimate Condition of Patentability (John F. Witherspoon ed., 1980). The term "prior art" is used to encompass, inter alia, all patents and printed publications that were publicly available at the time a particular patent application was filed. *See, e.g.*, Grubb, *supra* note 25, at 486.

38. 35 U.S.C. § 103(a).

39. *See generally* Graham v. John Deere Co., 383 U.S. 1 (1966). The Supreme Court in 1965 granted certiorari in the first three patent cases involving the standard of invention since the enactment of the 1952 Patent Act. *See* Chisum, *supra* note 16, § 5.02[5], at 5-37 (noting that the Supreme Court granted certiorari in 1965 in each of the patent cases: *Graham*, 383 U.S. 1; *Calmar, Inc. v. Cook Chem. Co.*, 383 U.S. 1 (1966); and *United States v. Adams*, 383 U.S. 39 (1966)).

40. *See* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007) (confirming that the obviousness analysis set forth in *Graham* "continue[s] to define the inquiry that controls").

41. *See Graham*, 383 U.S. at 17–18 ("While the ultimate question of patent validity is one of law, the § 103 condition . . . lends itself to several basic factual inquiries." (citation omitted)); *see also KSR*, 127 S. Ct. at 1745 ("The ultimate judgment of obviousness is a legal determination." (citing *Graham*, 383 U.S. at 17)).

recent appraisal of the obviousness analysis,[42] the *Graham* Court crafted "an expansive and flexible approach" intended to facilitate courts' application of § 103.[43] In particular, *Graham* enumerated several factual inquiries that underpin each legal obviousness determination: "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved."[44] Analysis based on these *Graham* factors, together with the evaluation of any objective evidence, or "secondary considerations,"[45] controls the question of obviousness.[46]

2. Pharmaceutical Obviousness and "Obvious to Try"

Section 103 serves as the legal nonobviousness foundation common to all areas of patent law, but its application may vary by technological discipline. For example, Professors Dan L. Burk and Mark A. Lemley contend,[47] and others agree,[48] that patent law is technology specific—e.g., inventions in the software field must clear a higher nonobviousness hurdle than inventions in the biotechnology field.[49] Regardless of how pharmaceuticals may compare with these disciplines,[50] obviousness is undoubtedly a hotly

42. In *KSR*, the Supreme Court addressed an obviousness subtest known as the "teaching, suggestion, or motivation" test, developed by the Federal Circuit to enable the obviousness inquiry in cases involving, inter alia, the combination of multiple prior art references. *See* 127 S. Ct. at 1734. The Court held that this test is not necessarily erroneous provided it is not applied as a "rigid rule." *Id.* at 1741. Other aspects of *KSR* are discussed in Part I.C.

43. *See KSR*, 127 S. Ct. at 1739 ("*Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive.").

44. *See Graham*, 383 U.S. at 17.

45. *Id.* at 17–18 (holding that relevant "secondary considerations" may include "commercial success, long felt but unsolved needs, failure of others, etc.").

46. *See, e.g.*, *KSR*, 127 S. Ct. at 1734.

47. *See generally* Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 Berkeley Tech. L.J. 1155, 1158–86 (2002) [hereinafter Burk & Lemley, *Technology-Specific*]; *accord* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1593 (2003) [hereinafter Burk & Lemley, *Policy Levers*].

48. *See, e.g.*, Mark D. Janis, Comment, *Equilibrium in a Technology-Specific Patent System*, 54 Case W. Res. L. Rev. 743 (2004); *see also* R. Polk Wagner, *Of Patents and Path Dependency: A Comment on Burk and Lemley*, 18 Berkeley Tech. L.J. 1341, 1343–45 (2003) (commenting that "Burk and Lemley are undoubtedly correct in noting that there is technological-specificity in the patent law," but further distinguishing between "micro-specificity" and "macro-specificity").

49. Burk and Lemley argue that appellate courts have applied a "rather strict standard" for obviousness in the context of software patents, whereas, by contrast, biotechnology inventors are "shielded from obviousness" due to an elevated requirement for explicit prior art disclosure in that field. Burk & Lemley, *Technology-Specific*, *supra* note 47, at 1167, 1181; *see also* Burk & Lemley, *Policy Levers*, *supra* note 47, at 1593 ("[T]he Federal Circuit has gone to inordinate lengths to find biotechnological inventions nonobvious . . . . [Yet] the court has imposed stringent enablement and written description requirements on biotechnology patents . . . . In computer software cases, the situation is reversed.").

50. Burk and Lemley noted that while their analysis focused on biotechnology and computer software as "two extreme examples" of the technology-specific nature of patent

contested subject in the pharmaceutical discipline, partly due to the aforementioned propensity for structural similarity among different active pharmaceutical ingredients.[51]

Through decades of litigation surrounding marketed pharmaceuticals and other chemical products, courts have fleshed out the statutory standard of obviousness in the context of small-molecule chemistry.[52] In instances where a claimed pharmaceutical compound has a structure and utility similar to a prior art compound, some courts have found the claimed compound to be prima facie obvious, thereby shifting the burden to the patentee to demonstrate evidence supporting the claimed compound's nonobviousness.[53]

Related to the question of whether two pharmaceutical compounds are structurally similar is the issue of whether a claimed pharmaceutical

law application, their approach "may have application to . . . small-molecule chemistry," such as pharmaceuticals. Burk & Lemley, *Technology-Specific*, *supra* note 47, at 1156.

51. *See supra* notes 1–8 and accompanying text.

52. *See, e.g.*, *In re* Papesch, 315 F.2d 381, 386–91 (C.C.P.A. 1963). *Papesch* discussed the "Hass-Henze doctrine," a pre–Patent Act common law patentability guide whereby "proof of the existence of unobvious or unexpected beneficial properties in a new compound, which would otherwise appear to be obvious . . . , is indicative of . . . patentability." *Id.* at 386. Recounting the historical application of the Hass-Henze doctrine both before and after the enactment of § 103, *Papesch* then specifically related this judge-made doctrine to the language of § 103, holding that, "'[i]n determining whether the claimed compounds are obvious within the meaning of 35 U.S.C. § 103, we think their properties may and should be considered.'" *Id.* at 390–91 (emphasis omitted) (quoting *In re* Petering, 301 F.2d 676, 683 (C.C.P.A. 1962); *see also* Chisum, *supra* note 16, § 5.04[6][b]–[f] (discussing the Hass-Henze doctrine, *Papesch*, and subsequent cases developing obviousness in the context of chemical similarity).

53. *See, e.g.*, *In re* Dillon, 919 F.2d 688, 692–94 (Fed. Cir. 1990) (holding tetra-orthoester fuel additive compounds prima facie obvious in view of structurally similar prior art compounds, and affirming the obviousness rejection based on a lack of evidence of unexpected properties); *In re* Chupp, 816 F.2d 643, 645–46 (Fed. Cir. 1987) (reversing the obviousness rejection of a structurally similar herbicide compound in light of demonstrated enhanced selectivity, since "[e]vidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness"); *In re* Grabiak, 769 F.2d 729, 731–32 (Fed. Cir. 1985) (declining to find a "'close' structural similarity" despite a difference of only one atom between a claimed herbicidal additive compound and a prior art compound); *In re* Payne, 606 F.2d 303, 313–14 (C.C.P.A. 1979) (holding a claimed heterocyclic compound obvious in light of structurally similar prior art compound with similar pesticidal activity based on "the expectation [of the skilled artisan] that compounds similar in structure will have similar properties"); *In re* May, 574 F.2d 1082, 1092–94 (C.C.P.A. 1978) (rebutting prima facie obviousness based on a structurally similar prior art isomer upon a showing of a claimed compound's unexpected lack of undesirable addiction properties); *In re* Wiechert, 370 F.2d 927, 928–33 (C.C.P.A. 1967) (holding a claimed testosterone derivative compound prima facie obvious over a structurally similar prior art compound where both compounds had similar utilities, but finding the claimed compound nonobvious in light of its demonstrated sevenfold improvement in activity); *Papesch*, 315 F.2d at 391–92 (finding evidence of anti-inflammatory activity sufficient to rebut prima facie obviousness of a claimed trialkyl compound over a structurally similar prior art homologue); *cf.* Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966) (holding that "secondary considerations" that can serve as indicia of nonobviousness include evidence of commercial success, long-felt but unsolved needs, and the failure of others, among other factors).

compound would have been obvious to try in light of the prior art. The obvious-to-try test is most contentiously employed when, upon finding any secondary indicia of nonobviousness insufficient, a court determines legal obviousness based only on the finding that it would have been obvious for a skilled artisan to try to make the invention.[54] In the pharmaceutical field, the obvious-to-try inquiry is often formulated as the allegation that it would have been obvious to try to modify a prior art pharmaceutical compound chemically to arrive at the claimed, structurally similar compound.[55]

Importantly, the obvious-to-try test discounts evidence indicating whether a person of ordinary skill in the art would have possessed any "reasonable expectation of success" of obtaining a beneficial physical, chemical, or biological effect upon performing the modification in question.[56] Such evidence has long been an important component of obviousness determinations in the chemical and pharmaceutical arts.[57]

54. *See* Chisum, *supra* note 16, § 5.04[1][f], at 5-318 (discussing "obvious to try" and noting that, when an "inventor selects a particular configuration from a broad range of possibilities suggested by the prior art[,] . . . [i]t is clear that the result achieved must be considered as well as the actual physical modification").

55. *See, e.g.*, *infra* Part II.A–B (discussing Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350 (Fed. Cir. 2007); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007)); *cf. In re* O'Farrell, 853 F.2d 894, 902–04 (Fed. Cir. 1988) (discussing "obvious to try" in the context of biotechnology).

56. *See* Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 High Tech. L.J. 1, 40–42 (1992). Professor Robert P. Merges asserts that "obvious to try" is a subset of "the reasonable expectation of success standard." *Id.* at 42. 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. *Id.* A finding of obviousness despite the lack of a reasonable expectation of success constitutes application of the "obvious to try" standard. *See id.*; *see also, e.g.*, *In re* Eli Lilly & Co., 902 F.2d 943, 945 (Fed. Cir. 1990) ("An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued."); *O'Farrell*, 853 F.2d at 902–04; *cf. In re* Pantzer, 341 F.2d 121, 124–26 (C.C.P.A. 1965). In *Pantzer*, the court conceded that an examiner's use of obvious-to-try phrasing in an obviousness rejection "leaves something to be desired." *Id.* at 124–25. Nevertheless, the court ultimately upheld the rejection under § 103 after finding that the invention's alleged superior properties would have been "expected" based on the teaching of numerous prior art references. *Id.* at 125–26. Employing reasoning akin to the "reasonable expectation of success" analysis, *see infra* note 57, the court noted that "obviousness does not require absolute predictability" and that "an invention can be said to be obvious if one ordinarily skilled in the art would consider that it was logical to anticipate with a high degree of probability that a trial of it would be successful," *id.* at 126.

57. *See* Richard J. Warburg, Note, *From Chemicals to Biochemicals: A Reasonable Expectation of Success*, 24 Suffolk U. L. Rev. 155, 172–73 (1990) (citing cases illustrating the close relationship between "reasonable expectation of success" and "predictability" for inventions involving new chemical compounds); *see also, e.g.*, Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (noting that a reasonable expectation of success supports a conclusion of obviousness); *In re* Longi, 759 F.2d 887, 897 (Fed. Cir. 1985) (concluding that evidence illustrating a reasonable expectation of success sufficiently supports an obviousness conclusion); *In re* Clinton, 527 F.2d 1226, 1228–29

Though not rigidly defined and admittedly "somewhat vague,"[58] a reasonable expectation of success falls somewhere between "absolute predictability"[59] and a mere "general incentive" to conduct research in a particular area.[60] By failing to probe meaningfully the existence of a

(C.C.P.A. 1976) ("Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." (emphasis omitted) (citation omitted)); *Pantzer*, 341 F.2d at 126 (holding that obviousness is properly established where one of ordinary skill could logically anticipate "with a high degree of probability," though not necessarily with "absolute predictability," that the invention "would be successful").

58. *See* Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a *certainty* of success.").

59. Absolute predictability is a concept foreign to much of the pharmaceutical arts. The biological effects of a chemical substance on the human body depend on a large number of interrelated variables, and the complexity and cost of modern-day clinical trials attest to the fundamental unpredictability in this field. *See* Dennis W. Raisch & Linda A. Felton, *The New Drug Approval Process and Clinical Trial Design*, *in* Remington: The Science and Practice of Pharmacy 965, 965 (David B. Troy ed., Lippincott Williams & Wilkins 21st ed. 2006) (1885). In reviewing the various stages of drug development and regulatory approval, Raisch and Felton remarked,

> The research and development efforts needed to ensure the safety and efficacy of new drugs are complex, time consuming, and financially risky. Thousands of compounds undergo extensive testing for every one new chemical that receives marketing approval. . . . [O]nly 30% of drugs that reach the marketplace generate sufficient revenue to recover the average cost of its development.

Id.; *cf.* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151, 165–67 (2003) (estimating the total average cost of developing a drug to be approximately $802 million, of which approximately $467 million represents clinical trial expenditures). Many of the nonbiological properties of a drug are also largely unpredictable. For example, despite significant ongoing research efforts, the particular crystal form that a drug adopts remains generally unpredictable. *See, e.g.*, Andrew V. Trask, *An Overview of Pharmaceutical Cocrystals as Intellectual Property*, 4 Molecular Pharmaceutics 301, 305–06 (2007), *available at* http://pubs.acs.org/cgi-bin/sample.cgi/mpohbp/2007/4/i03/pdf/mp070001z.pdf (discussing the general unpredictability of pharmaceutical crystal structures and implications for patentability); *see also* G.M. Day et al., A Third Blind Test of Crystal Structure Prediction, B61 Acta Crystallographica 511, 525–26 (2005) (summarizing results of a blind crystal structure prediction test, and noting that, for the most part, "the overall success rates remain poor"). The crystal form of a drug can impact a broad range of its physical and chemical properties, including solubility and stability, and can affect its amenability to successful manufacture and formulation. *See, e.g.*, Stephen R. Byrn et al., Solid-State Chemistry of Drugs 14–15 (2d ed. 1999) (listing numerous physical and chemical properties that depend upon a drug's solid-state structure, including its crystal form).

60. *See, e.g.*, *In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("'Obvious to try' has long been held not to constitute obviousness. A general incentive does not make obvious a particular result . . . ." (citation omitted)); Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989) ("'[A]bsolute predictability of success' is not the criterion; '[f]or obviousness under § 103, all that is required is a reasonable expectation of success.'" (second alteration in original) (quoting *O'Farrell*, 853 F.2d at 903)); *see also In re* Longi, 759 F.2d 887, 897 (Fed. Cir. 1985) ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness."). To recite one specific example, the *O'Farrell* court held that a prior art reference, which "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful," provided a skilled artisan with a reasonable expectation of success. *O'Farrell*, 853 F.2d at 902.

reasonable expectation of success, the obvious-to-try test risks invalidating patents covering significant innovations in cases where the researcher merely pursued a "promising field of experimentation" without specific prior art guidance as to the particular form of the invention or how to achieve it.[61]

Raising the level of patentability to this extent could substantially alter the incentive for experimentation, specifically in areas where a prior art reference even remotely suggested attempting a particular research endeavor.[62] On the other hand, conferring undue credit on an experiment's unpredictability could weaken the nonobviousness patentability criterion in the pharmaceutical arts.[63] Such contrary viewpoints regarding the obvious-to-try test exemplify an ongoing conflict in the patent system—promoting innovation while maintaining competition—which serves to maximize public benefit from research-based inventions.[64]

B. *Evolution of the Obvious-to-Try Patentability Standard*

The obvious-to-try test, which discounts an absence of any reasonable expectation of success, has long been maligned by courts.[65] This opposition may be changing, however, as indicated by several court decisions, including the Supreme Court case of *KSR International Co. v. Teleflex Inc.*,[66] discussed below.[67] To understand the extent to which courts have more warmly embraced the obvious-to-try standard, this section

61. *See O'Farrell*, 853 F.2d at 903 (noting that applying the obvious-to-try test would invalidate an invention that involved "explor[ing] a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it").

62. *See, e.g.*, *In re* Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966) ("[P]atentability determinations based on [the obvious-to-try] test would . . . result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.'").

63. *See, e.g.*, *O'Farrell*, 853 F.2d at 903 (noting that "for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice," and because there is "always at least a possibility of unexpected results," requiring absolute predictability would render "apparently obvious" inventions legally nonobvious).

64. *See, e.g.*, Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 146 (1989) ("The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'"). *See generally* FTC, To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy ch. 3(II)(C)–(D) (2003), *available at* www.ftc.gov/os/2003/10/innovationrpt.pdf (noting the importance of both patent protection and competition to promote innovation in the pharmaceutical industry).

65. *See* Merges, *supra* note 56, at 40 ("Since the early 1960's the courts have been ruling consistently that 'obvious to try' is not the standard of patentability."); Bertram I. Rowland, *Obvious to Try—A Nonstandard of Patentability*, *in* Nonobviousness—The Ultimate Condition of Patentability, *supra* note 37, pt. 7, at 201, 201 ("A standard of patentability under 35 U.S.C. § 103 of 'obvious to try' has generally not received a cordial welcome in the courts.").

66. 127 S. Ct. 1727 (2007); *see also* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007). *But see* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350 (Fed. Cir. 2007).

67. *See infra* Part I.C.

provides a historical overview of this "nonstandard" of patentability.[68] As this analysis indicates, if indeed the Supreme Court in *KSR* breathed life into "obvious to try" as a patentability standard,[69] the Court would not be forging new ground, but rather would be reclaiming old territory abandoned by the statutory adoption of the nonobviousness requirement.

1. Prior to the Patent Act of 1952

The 1952 Patent Act set forth the concept of nonobviousness as a statutory requirement for patentability.[70] Nevertheless, in the decade prior to its enactment, reasoning analogous to the obvious-to-try standard constituted an acceptable approach for invalidating a patent claim. *In re Kepler*[71] was one early CCPA[72] decision presaging the modern obvious-to-try inquiry. In *Kepler*, the CCPA scrutinized the patentability of methods of forming multilayer vessels for withstanding high internal pressure.[73] In particular, the claims required stressing the vessel's outermost layer to provide a vessel of greater overall strength.[74] The court's analysis involved prior art methods that, according to the court, would have resulted in at least some (albeit possibly unintended) stressing of the outer layer.[75] The court affirmed the rejection of the U.S. Patent Office Board of Patent Appeals and Interferences (Patent Board), noting that, "[i]f a manufacturer of multi-layer vessels followed the teachings of the [prior art], it seems clear that his process might well involve every step which [the patentee] teaches."[76] Under modern patent law, the basis for this rejection might be recognized as anticipation,[77] or perhaps inherent anticipation.[78] The court's holding, however, used broad language in rejecting the claims: "A patent should not be granted for [the] discovery of a result that would flow naturally from the

68. *See, e.g.*, Merges, *supra* note 56, at 69 (denoting the "obvious-to-try" test as a "(non)standard" of patentability); Rowland, *supra* note 65, at 201 (referring to "obvious to try" as a "nonstandard of patentability"). *But see* Chisum, *supra* note 16, § 5.04[1][f], at 5-318 ("[I]n certain situations, obviousness is properly predicated on an obvious to try concept." (citing *O'Farrell*, 853 F.2d at 903)); *infra* notes 139–43 and accompanying text.

69. *KSR*, 127 S. Ct. at 1742 ("[T]he fact that a combination was obvious to try might show that it was obvious under § 103.").

70. Bryson Act (Patent Act), ch. 950, 66 Stat. 792 (1952) (codified as amended in scattered sections of 35 U.S.C.); *see also* Graham v. John Deere Co., 383 U.S. 1, 16 (1966) (remarking that § 103 codified judicial precedents embracing the patentability standard set forth in *Hotchkiss v. Greenwood*, 52 U.S. (11 How.) 248 (1851)). *See generally* Nonobviousness—The Ultimate Condition of Patentability, *supra* note 37.

71. 132 F.2d 130 (C.C.P.A. 1942).

72. The CCPA heard, inter alia, patentability appeals from the U.S. Patent and Trademark Office (PTO).

73. *Id.* at 131 (assessing the patentability of methods of forming multi-layer pressure vessels that are capable of withstanding high internal pressure).

74. *Id.* at 131–32.

75. *Id.* at 133.

76. *Id.*

77. *See* 35 U.S.C. § 102(a) (2000).

78. *See generally* Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371, 375–89 (2005) (discussing aspects of anticipatory inherency).

teachings of the prior art," regardless of whether the patentee "has made distinct and advantageous advances in the art."[79]

The invitingly expansive "flow naturally"[80] analysis of *Kepler* took root in a variety of patentability questions, including cases that would later be recognized as involving obvious-to-try issues.[81] In several instances, for example, the court invoked *Kepler* to dismiss evidence of unexpected results, since these results "flow[ed] naturally" from the claimed product or method that the prior art rendered obvious to try.

In one such case, *In re Leum*, the CCPA evaluated the validity of claims directed to an improved method of making the solvent toluene using a closed vessel under superatmospheric pressure.[82] In light of the prior art, the court noted that, "[w]hether or not the [prior art] systems were open or closed, it surely would [have been] obvious to try either in a reaction of the character defined by the patent."[83] Citing to *Kepler*, the court dismissed the relevance of any unexpected results: "If [the patented process] is within the skill of the art, there can be no invention even though the results obtained by the claimed process are better than those shown by [the prior] art."[84]

A later case, *In re Inman*, invoked the *Kepler* "flow naturally" analysis to affirm the invalidity of claims directed to a highly refined, chlorinated petroleum product.[85] The court held that, when a claimed product "was fairly suggested by the prior art," it did not matter that the invention "disclosed in [the] application is superior, and perhaps even unexpectedly superior to [the prior art product]."[86] Indeed, the court held that "such superiority does not constitute a basis for the issuance of a patent."[87]

The holding in *Kepler* formed a basis for invalidating claims to an invention that—although not specifically described in the prior art—were at least rendered obvious to try by the prior art teachings. *Kepler* therefore provided a rationale for setting aside evidence that a skilled artisan would not have had a reasonable expectation of success. As *Kepler* and other contemporaneous cases indicated, a claimed invention could be invalidated by showing that the invention would have been obvious to try.

79. *Kepler*, 132 F.2d at 133.

80. *Id.*

81. *See, e.g.*, *In re* Kelley, 230 F.2d 435, 439 (C.C.P.A. 1956) (holding that the modification of prior art air conditioning system is unpatentable despite "certain advantages," since "it is well settled that patentability may not be based on results which flow naturally from the teaching of the art" (citing *Kepler*, 132 F.2d 130)); *In re* Inman, 228 F.2d 226, 228 (C.C.P.A. 1955); *In re* Olsen, 146 F.2d 501, 502 (C.C.P.A. 1944) (holding that a dry-cleaning soap composition with an added ingredient is unpatentable, since, "[i]f the idea of adding [the ingredient] was an obvious one, the fact that the improvement may have exceeded expectations does not render it patentable" (citing *Kepler*, 132 F.2d 130)).

82. *In re* Leum, 158 F.2d 311 (C.C.P.A. 1946).

83. *Id.* at 312.

84. *See id.*

85. *Inman*, 228 F.2d 226.

86. *Id.* at 228.

87. *Id.*

The Supreme Court applied a similar approach in the 1948 case of *Mandel Bros. v. Wallace*.[88] In *Mandel Bros.*, the Court considered a patent directed to an improved antiperspirant that, in contrast to other products, neither irritated skin nor corroded clothing.[89] The specific improvement over the prior art involved the addition of urea, a base, to the acid salts of the antiperspirant composition.[90]

Arguing for nonobviousness, the patentee insisted that the prior art would have discouraged a skilled chemist from adding urea: "The natural conclusion of a chemist . . . would have been that urea would result in the same failure [as that of the prior art] if combined with the acid salts involved in his patent."[91] Instead, the patentee argued, the result "was a 'paradoxical' one, unpredictable by a skilled chemist."[92] The Court dismissed these arguments, however, noting that the purported innovation merely involved a "simple experiment."[93] The Court rested its obviousness conclusion on the finding that "the general store of chemical knowledge . . . was such that any one working on any problem of acidic corrosion and irritation would naturally and spontaneously have tried urea."[94] The holding in *Mandel Bros.* thus illustrates that, during the decade leading up to the Patent Act, the obvious-to-try rationale constituted a viable basis for negating patentability for lack of invention.

2. The 1952 Patent Act and Ensuing Developments

a. *The 1952 Patent Act*

The 1952 Patent Act heralded a new era of patentability jurisprudence. According to its coauthor, Judge Giles S. Rich, the Act was a reaction to "a perceived antagonistic attitude on the part of the judiciary toward patents."[95] Indeed, exemplifying this antipatent sentiment, Justice Robert H. Jackson, dissenting from the invalidation of a patent for lack of "invention," had remarked that "the only patent that is valid is one which this Court has not been able to get its hands on."[96] Section 103 of the

88. 335 U.S. 291 (1948).
89. *See id.* at 292–93.
90. *See id.*
91. *Id.* at 295.
92. *See id.*
93. *See id.*
94. *See id.* at 296.
95. *See* Giles S. Rich, *Why and How Section 103 Came to Be*, *in* Nonobviousness—The Ultimate Condition of Patentability, *supra* note 37, pt. 1, at 201, 201, *reprinted in* 14 Fed. Cir. B.J. 181, 186 (2004) (paper prepared for delivery at the Bureau of National Affairs' conference commemorating the twenty-fifth anniversary of 35 U.S.C. § 103 in September 1977).
96. *See* Jungersen v. Ostby & Barton Co., 335 U.S. 560, 572 (1949) (Jackson, J., dissenting); *see also* Brief Amicus Curiae in Support of 35 U.S.C. 103 at 2, Graham v. John Deere Co., 383 U.S. 1 (1966) (No. 11), 1965 WL 115655 (noting that, prior to the Supreme Court case of *Graham*, the U.S. Court of Appeals for the Eighth Circuit held "some 22

Patent Act, which implemented "non-obvious subject matter" as a "[c]ondition[] for patentability,"[97] replaced the "vague" requirement of "invention"[98] with the more concrete, objective requirement of nonobviousness.[99] Nonobviousness has since been termed "the ultimate condition of patentability."[100]

After its enactment, § 103 engendered disagreement over whether it forged a new patentability standard or simply codified prior judicial precedent. The Supreme Court has repeatedly stated that § 103 "was intended merely as a codification of judicial precedents"[101] yet has also acknowledged that Congress intended the second sentence of § 103 to abolish the "flash of creative genius" test used in an earlier Supreme Court decision.[102] Others, including Judge Rich, have supported the view that § 103 was not an explicit codification, but rather the expression of a unique patentability requirement that drew upon prior court decisions and public policy considerations.[103]

consecutive patents invalid," and the U.S. Court of Appeals for the Third Circuit found "32 [patents] invalid out of the last 33 before it").

97. 35 U.S.C. § 103 (2000). Section 103 is entitled "Conditions for patentability; non-obvious subject matter." *Id.*

98. The patentability requirement of "invention" sustained significant criticism before its replacement by the statutory requirement of nonobviousness. In 1891, the Supreme Court noted a number of unsatisfactory interpretations of the term "invention," ultimately concluding that the term "cannot be defined in such manner as to afford any substantial aid in determining whether a particular device involves an exercise of the inventive faculty or not." *See* McClain v. Ortmayer, 141 U.S. 419, 426–27 (1891). Famously, Judge Learned Hand proclaimed that "the question [of] whether there is a patentable invention . . . is as fugitive, impalpable, wayward, and vague a phantom as exists in the whole paraphernalia of legal concepts." Harries v. Air King Prods. Co., 183 F.2d 158, 162 (2d Cir. 1950).

99. 35 U.S.C. § 103.

100. *See, e.g.*, Nonobviousness—The Ultimate Condition of Patentability, *supra* note 37.

101. *See Graham*, 383 U.S. at 17. The *Graham* Court remarked that § 103 codified judicial precedents embracing the patentability standard set forth in *Hotchkiss*. *See id.* at 16–17. In *Hotchkiss*, the Supreme Court denied the patentability of improvements in making doorknobs and other types of knobs because the improvements consisted of components that "had been before known and used," involved a combination that "was simply the substitution of one material for another," and required "no more ingenuity or skill . . . than that possessed by an ordinary mechanic acquainted with the business." *Hotchkiss*, 52 U.S. (11 How.) at 264–65 (1851). Moreover, in *KSR International Co. v. Teleflex Inc.*, the Court reaffirmed that the "bar on patents claiming obvious subject matter [was] established in *Hotchkiss* and codified in § 103." 127 S. Ct. 1727, 1746 (2007); *see also* James W. Dabney, KSR*: It Was Not a Ghost*, 24 Santa Clara Computer & High Tech. L.J. 131, 131–34 (2007) (arguing that *KSR* reaffirms that § 103 codified the patentability standard set forth in *Hotchkiss*).

102. *See Graham*, 383 U.S. at 15 (quoting Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84, 91 (1941)).

103. *See* Giles S. Rich, *Laying the Ghost of the "Invention" Requirement*, 1 APLA Q.J. 26, 34–37 (1972) (arguing that § 103 "was a new statement of an old requirement of the law which was utterly uncertain and indefinite," and that "[t]he statute undertook to remove ambiguity and provide definiteness"); Brief Amicus Curiae in Support of 35 U.S.C. 103, *supra* note 96, at 6–7. Submitted by legal scholars E. Ernest Goldstein and Page Keeton, this amicus brief was "not presented in support of any result as to the submitted patent-in-suit." *Id.* at 1. The scholars argued that § 103 is "an original expression of a unique requirement for patentability," but conceded that the drafters "had in mind the opinion in *Hotchkiss v. Greenwood*." *Id.* at 6. They advocated giving "full meaning to the words of § 103 without

Regardless of whether Congress intended § 103 to serve primarily as a codification of judicial precedents, the 1952 Patent Act clearly triggered the ensuing impropriety of the obvious-to-try patentability standard. For example, § 103 requires that patentability be assessed by examining the claimed invention "as a whole."[104] With respect to chemical and pharmaceutical inventions, this requirement mandates that, for purposes of patentability, the structure of a chemical compound is inseparable from its properties.[105] Thus, focusing on whether a particular structural modification to a pharmaceutical would have been obvious to try, while disregarding whether such a modification would have been accompanied by a reasonable expectation of associated beneficial properties, contravenes the "as a whole" requirement of § 103.[106]

Moreover, the concluding sentence of § 103(a) warns that "[p]atentability shall not be negatived by the manner in which the invention was made."[107] In his dissenting opinion in *In re Merck & Co.*, Judge Philip B. Baldwin considered the meaning of this statutory requirement.[108] By recalling Congress's intent in adopting this provision,[109] Judge Baldwin concluded that Congress enacted the second sentence of § 103 so as to reject the obvious-to-try test: "Obvious-to-try is not the test for patentability under 35 U.S.C. § 103. This court and its predecessor, the CCPA, have repeatedly rejected that approach. Congress has also rejected that approach by

distortion by prior divergent judicial writings." *Id.* at 7; *see also* Robert P. Merges, *One Hundred Years of Solicitude: Intellectual Property Law, 1900–2000*, 88 Cal. L. Rev. 2187, 2222–23 (2000) ("[The 1952 Patent Act] was not simply the capstone to a steady project of doctrinal construction. It overwrote some critical anti-patent decisions of the Supreme Court from its most virulent anti-patent era . . . . [Section 103], though supposedly a mere restatement of existing principles, in actuality contained language aimed specifically at softening certain Supreme Court opinions from the 1940s . . . .") (citations omitted)).

104. *See* 35 U.S.C. § 103(a); *see also* Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 (Fed. Cir. 1984) ("The proper approach to the obviousness issue must start with the claimed invention *as a whole*." (citing 35 U.S.C. § 103)).

105. *See In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963) ("[B]oth before and after the enactment of section 103, [courts] have determined the unobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties. . . . From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."); *see also In re* Sullivan, 498 F.3d 1345, 1352–53 (Fed. Cir. 2007) (vacating and remanding the Patent Board's obviousness holding for failure to consider purported unexpected property); *In re* Dillon, 919 F.2d 688, 693 (Fed. Cir. 1990) ("There is no question that all evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability . . . .").

106. *See, e.g.*, *In re* Huellmantel, 324 F.2d 998, 1001 n.3 (C.C.P.A. 1963) ("Nothing is said [in § 103] about 'obvious *to try*.' Consideration of the subject matter 'as a whole' in chemical cases requires comparison of properties, pharmaceutical or otherwise, as well as comparison of chemical structures.").

107. 35 U.S.C. § 103(a).

108. *See In re* Merck & Co., 800 F.2d 1091, 1099–1100 (Fed. Cir. 1986) (Baldwin, J., dissenting).

109. "The reviser's note on this sentence states 'it is immaterial whether it resulted from long toil and experimentation or from a flash of genius.'" *Id.* at 1100.

enacting the second sentence of 35 U.S.C. § 103 . . . ."[110] As Judge Baldwin suggested, and as the following analysis illustrates, the CCPA slowly but deliberately retreated from the obvious-to-try patentability test following the enactment of § 103.

b. *Growing Impropriety of "Obvious to Try"*

Following the enactment of § 103, the CCPA determined obviousness by increasingly pondering the expectations of the skilled artisan. One early decision, *In re Eisenhut*, involved the invention of a new process for preparing a material resembling woven cloth.[111] In rejecting the claims as unpatentable, the court noted that the invention "would require no more than simple experimentation by the skilled artisan."[112] Despite affidavits contending that comparative test data, submitted in support of patentability, indicated that the invention "must be considered as unexpected and surprising to the man skilled in the art," the CCPA maintained that "we have not been shown that unexpected results were in fact obtained."[113] The *Eisenhut* court at least considered the expectations of a person skilled in the art, but it ultimately fell back to the rationale of *In re Kepler*,[114] which held that one cannot patent "a result that would flow naturally from the application of the teachings of the prior art."[115]

Several years later, the obvious-to-try test sustained direct criticism in *In re Huellmantel*, a case involving the obviousness of an anti-inflammatory pharmaceutical combination.[116] In an impassioned footnote, Judge Rich felt "compelled" to criticize the obvious-to-try test on which the Patent Board had relied.[117] He noted that in § 103 "[n]othing is said about 'obvious to try.' Consideration of the subject matter 'as a whole' in chemical cases requires comparison of properties, pharmaceutical or otherwise, as well as comparison of chemical structures."[118] Nonetheless,

110. *See id.* at 1099–1100 (citations omitted).

111. *See In re* Eisenhut, 245 F.2d 481, 486 (C.C.P.A. 1957) (affirming the rejection of claims directed to a process for preparing a material resembling woven cloth from a carded fleece fiber, the greater portion of which consisted of regenerated cellulose fibers).

112. *Id.* at 485.

113. *Id.* at 486.

114. 132 F.2d 130, 133 (C.C.P.A. 1942) ("A patent should not be granted for [the] discovery of a result that would flow naturally from the teachings of the prior art," regardless of whether the patentee "has made distinct and advantageous advances in the art.").

115. *Eisenhut*, 245 F.2d at 486; *see also supra* notes 80–81 and accompanying text.

116. *See In re* Huellmantel, 324 F.2d 998 (C.C.P.A. 1963).

117. *See id.* at 1001 n.3.

118. *Id.*; *see also supra* notes 104–06 and accompanying text. Judge Giles S. Rich continued,

> We do not mean to imply that every variance in property of a new compound or composition will tip the balance for patentability where otherwise closely related compounds or compositions are involved. However, all relevant property differences *must be considered* in the light of the facts of each case in the determination of statutory obviousness.

Huellmantel, 324 F.2d at 1001 n.3.

on account of the positive results evident in the prior art, the court perceived "no reason why one skilled in this art would not expect even better results" with the claimed pharmaceutical composition, and affirmed the Patent Board's decision.[119]

In general, the CCPA's obvious-to-try decisions following the enactment of § 103 fluctuated with respect to the weight accorded to evidence of the skilled artisan's expectation of success.[120] The court's decisions during this period accurately reflect what Judge Rich later termed a "slow transition" from the common law requirement of "invention" to the statutory test for nonobviousness.[121]

c. *Rejection of "Obvious to Try" as a Patentability Standard*

After a long period of silence on the subject,[122] the obviousness issue attracted the Supreme Court's attention in the 1966 case of *Graham v. John Deere Co.*[123] In setting forth the present-day nonobviousness analysis,[124]

119. *Id.* at 1003.

120. *Compare, e.g.*, *In re* Novak, 306 F.2d 917, 921–23 (C.C.P.A. 1962) (affirming obviousness since it would have been "obvious to try reactions previously successful [in the prior art] . . . with at least a reasonable expectation of success" (quoting the examiner's rejection)), *with In re* Sejournet, 285 F.2d 823, 825–26 (C.C.P.A. 1961) (affirming obviousness using the obvious-to-try test, holding that "it would have been obvious to try in view of the teachings of the prior art," despite evidence of objective expectations, and finding it "unnecessary to consider" the applicant's "new and unexpected results"), *and In re* Ruscetta, 255 F.2d 687, 692 (C.C.P.A. 1958) (affirming obviousness since "it would be most obvious to one skilled in the art, in view of [the prior art], to apply the same . . . process [as the invention]" and noting that "one would not be surprised if [the invention worked]").

121. *See* Rich, *supra* note 103, at 37. Judge Rich commented, "When I came to the CCPA in 1956, three and a half years after Section 103 came into effect, I found it being totally ignored." *Id.* He attributed the CCPA's lethargic adoption of the § 103 nonobviousness requirement to the fact that, for some years, the court continued to evaluate PTO rejections and appellants' briefs were still couched in terms of an "invention" requirement. *See id.*

122. *See* Edmund W. Kitch, Graham v. John Deere Co.*: New Standards for Patents*, 1966 Sup. Ct. Rev. 293, 293 ("In the 1964 Term, it was news of importance to the patent bar, though of little note elsewhere, that the Supreme Court had, for the first time in fifteen years, undertaken to review some patent cases turning on the issue of invention.") (footnote omitted)).

123. 383 U.S. 1, 3 (1966) (noting that, in *Graham*, the Court considered the statutory obviousness test for the first time). Historically, the Supreme Court has been generally reluctant to hear patent cases. *See* Arthur J. Gajarsa & Lawrence P. Cogswell III, Foreword, *The Federal Circuit and the Supreme Court*, 55 Am. U. L. Rev. 821, 822 (2006) (noting that, since the inception of the Federal Circuit in 1982, the Supreme Court has granted certiorari in only sixteen patent cases); *see also* Mark D. Janis, *Patent Law in the Age of the Invisible Supreme Court*, 2001 U. Ill. L. Rev. 387, 387 (contending that "[t]he Supreme Court has rendered itself well nigh invisible in modern substantive patent law" and that, as a result, the Federal Circuit "has become the de facto supreme court of patents"). *But see* Gregory A. Castanias et al., *Survey of the Federal Circuit's Patent Law Decisions in 2006: A New Chapter in the Ongoing Dialogue with the Supreme Court*, 56 Am. U. L. Rev. 793, 813–14 (reviewing recent case law indicating "the Supreme Court's apparently enhanced interest in the patent law jurisprudence of the Federal Circuit," and arguing that "an era of active U.S. Supreme Court review of Federal Circuit decisions is upon us").

124. *See supra* text accompanying notes 39–46.

the *Graham* Court included the consideration of helpful objective evidence, or "secondary considerations,"[125] in assessing obviousness. Subsequent court decisions have elaborated upon such relevant objective evidence to include unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing agreements, and the skepticism of experts.[126] *Graham* did not directly address the obvious-to-try test, but by emphasizing the consideration of relevant objective evidence, the Court may nevertheless have affirmed the impropriety of this patentability standard. After all, the objective evaluation of "unexpected" results entails an assessment of the expectations of a person of ordinary skill—which, in effect, sidesteps the obvious-to-try test.

The CCPA's distaste for the obvious-to-try test intensified following the Supreme Court's pronouncement in *Graham*. *In re Tomlinson* implicitly followed Judge Rich's earlier *Huellmantel* footnote commentary, flatly rejecting "obvious to try" as an acceptable patentability standard.[127] At issue in *Tomlinson* were product and process claims to compositions of the polymer polypropylene containing particular metallic salts which improved the compositions' photostability.[128] The Patent Board affirmed the examiner's claim rejection, agreeing with the examiner that "'it would be obvious for a skilled chemist to try to stabilize polypropylene'" using compounds known to stabilize the chemically related polymer polyethylene.[129] In response, the court asserted:

> [T]here is usually an element of "obviousness to try" in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research."[130]

125. *See Graham*, 383 U.S. at 17–18 (holding that relevant "secondary considerations," include "commercial success, long felt but unsolved needs, failure of others, etc.," and that such considerations "may have relevancy" as indicia of obviousness or nonobviousness).

126. *See, e.g.*, Allen Archery, Inc. v. Browning Mfg. Co., 819 F.2d 1087, 1092 (Fed. Cir. 1987) (noting that obviousness requires factual inquiries into the three *Graham* factors in addition to "any objective evidence of non-obviousness, such as long-felt need, commercial success, failure of others, copying, and unexpected results"); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983) ("[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness. Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record." (citations omitted)).

127. *See In re* Tomlinson, 363 F.2d 928, 931–32 (C.C.P.A. 1966).

128. *See id.* at 930–31.

129. *See id.* at 931 (quoting the examiner's rejection). The examiner further noted that "it would be 'routine experimentation for a skilled chemist to . . . try[] the known stabilizers for polyethylene.'" *Id.* (quoting the examiner's rejection). The examiner cited to *In re Moreton*, 288 F.2d 940 (C.C.P.A. 1961), for the proposition that obviousness does not require absolute predictability. *See id.*

130. *Id.* at 931.

The court ultimately overturned the obviousness rejection of certain disputed claims in view of evidence showing the art to be "quite empirical" and that "[n]early every reference of record speaks of the unexpectedness of the behavior of 'related' materials."[131] In essence, the court held that despite the structural similarity between the two polymers, a chemist of ordinary skill would not have had a reasonable expectation of success that the metallic salt stabilizers that worked for polyethylene would also work for polypropylene.

Ensuing cases generally followed the *Tomlinson* rationale, thereby rejecting the obvious-to-try test. In his concurring opinion in *In re Dien*, Judge Arthur M. Smith of the CCPA noted disapprovingly that "[t]he examiner, in applying section 103, cast his inquiry in terms of 'obvious to try.'"[132] Citing to *Tomlinson*, he continued, "There is, of course, nothing in the statute which permits application of such a test."[133] Following *Dien*, the CCPA addressed the broader policy implications of the obvious-to-try test in *In re Lindell*, a case involving the chemical composition of an electrical circuit.[134] Citing *Tomlinson*, the court noted that "application of the 'obvious to try' test would often deny patent protection to inventions growing out of well-planned research which is, of course, guided into those areas in which success is deemed most likely. . . . But resulting inventions are not necessarily obvious. Serendipity is not a prerequisite to patentability."[135] The growing consensus regarding the impropriety of the obvious-to-try test relegated much of the discussion of the test to appellants' briefs (e.g., where appellants argued that a claim rejection was founded on the impermissible obvious-to-try standard) and dissenting opinions (e.g., where the dissenting judge viewed the majority as according insufficient weight to evidence that a skilled artisan would not have possessed a reasonable expectation of success).[136]

131. *See id.* at 933. The court affirmed the rejection of certain of the claims as anticipated by a particular prior art reference, but characterized the rejection as "highly technical" and "not based on any real teaching of the effect of nickel salts on stabilization against ultraviolet light." *Id.* at 934.

132. *See In re* Dien, 371 F.2d 886, 889 (C.C.P.A. 1967) (Smith, J., concurring).

133. *Id.* (noting that the obvious-to-try test "not only involves an analysis for which there is no authorization but it precludes a consideration of the invention as a whole for which there is an explicit statutory directive").

134. *See In re* Lindell, 385 F.2d 453 (C.C.P.A. 1967).

135. *Id.* at 455.

136. For example, in *In re Carey* a majority of the court determined that a claimed method of combating a urinary tract infection was obvious and unpatentable. 392 F.2d 646, 647 (C.C.P.A. 1968). The claimed method involved orally administering a compound designated "NF-246." *Id.* at 646–47. Prior art included the use of NF-246 for certain bacterial infections and the use of a structurally similar compound for urinary tract infections. *See id.* at 647. The dissenting opinion of Judge Arthur M. Smith argued that, even if one skilled in the art were "led to experiment with NF-246" with urinary tract infections, "he would not expect to find" the good results presented by the applicant. *See id.* at 652 (Smith, J., dissenting). Judge Smith supported his position by noting that "[t]he court has often stated its basic disagreement with an 'obvious to try analysis' under 35 U.S.C. § 103." *Id.* at 652 n.1. Other decisions involving structurally similar chemical compounds, including pharmaceuticals, followed a trajectory like that of *Carey*. For example, in *In re*

By the late 1970s, attempts by the Patent Board to argue for obviousness based on the obvious-to-try standard had all but disappeared,[137] and any discussion of the obvious-to-try test generally focused on its alleged misapplication. Among the most prominent post-*Graham*, pre-*KSR*[138] cases forsaking the obvious-to-try test was *In re O'Farrell*, a case involving an invention in the field of biotechnology.[139] Reiterating that "'obvious to try' [is] a standard which this court and its predecessors have repeatedly rejected as improper grounds for a § 103 rejection,"[140] the court noted that "the meaning of this maxim is sometimes lost."[141] The court then offered two alternative meanings for the term "obvious to try," both of which were characterized by the absence of any reasonable expectation of success.[142] Indeed, the court held that the references under consideration in *O'Farrell* provided a reasonable expectation of success—thus finding the two aforementioned obvious-to-try scenarios inapplicable.[143]

The Federal Circuit employed the *O'Farrell* "obvious to try" dicta to the facts of *In re Deuel*, thereby extending the impropriety of the obvious-to-try test to the field of biotechnology.[144] In *Deuel*, the Federal Circuit considered whether the existence of general cloning techniques, coupled

Merck & Co. the court weighed evidence of whether a skilled researcher would have possessed a reasonable expectation of success upon making the necessary chemical changes. 800 F.2d 1091, 1097 (Fed. Cir. 1986). The majority held that the claimed compound was rendered obvious by a structurally similar prior art compound with a similar utility. *See id.* at 1099. In dissent, Judge Philip B. Baldwin argued that the majority erred by applying the obvious-to-try test in an uncertain field of research. *See id.* at 1099–1101 (Baldwin, J., dissenting).

137. *See, e.g.*, Rowland, *supra* note 65, at 201 ("The [obvious-to-try] question seems to arise most frequently with respect to chemical compounds which are new and useful but structurally similar to old compounds.").

138. *See infra* Part I.C.

139. *See In re* O'Farrell, 853 F.2d 894, 901–04 (Fed. Cir. 1988). The court in *In re O'Farrell* held that claims to a method of producing a predetermined protein in a host bacteria by expressing a cloning vector containing a linked heterologous gene were obvious in light of the applicants' own prior art publication describing "virtually everything in the claims." *Id.* at 901.

140. *Id.* at 902.

141. *Id.* at 903.

142. *See id.*

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id. (citations omitted).

143. *See id.* at 903–04 ("Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success."); *see also In re* Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." (citations omitted)).

144. *See In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

with the knowledge of a protein's structure, might have made it obvious to prepare the particular compound at issue, a type of DNA.[145] While acknowledging the possibility that the prior art "might have . . . made it obvious to prepare a cDNA," the court noted that "'[o]bvious to try' has long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."[146] On this basis, the court reversed the Patent Board's obviousness rejection of the claims.[147]

C. KSR v. Teleflex*: The Supreme Court Weighs In*

The 2007 Supreme Court decision of *KSR International Co. v. Teleflex Inc.*[148] represented a long-awaited return of the Supreme Court to the issue of obviousness.[149] In the short term, *KSR* appears to have injected as many questions as answers into the debate over legal obviousness,[150] including those related to the proper application of the obvious-to-try test. As discussed above, prior to *KSR*, the Federal Circuit repeatedly cautioned that the obvious-to-try test was an improper basis for determining obviousness.[151] Notwithstanding this seemingly uniform discontent with the obvious-to-try standard of patentability, *KSR* revisited the test, seemingly recasting it in a more favorable light.[152] In assessing the obviousness of an automobile accelerator pedal equipped with an electronic sensor, the Supreme Court in *KSR* commented that the Federal Circuit "conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"[153] In

145. *See id*. The compound at issue in *Deuel* was a complementary DNA (cDNA) macromolecule that encoded a protein involved in cellular reproduction. *See id.* at 1554.

146. *Id.* at 1559 (citation omitted) (emphasis omitted).

147. *See id.* at 1560.

148. 127 S. Ct. 1727 (2007). See *supra* note 42 for a brief discussion of the primary issue in *KSR*. *See also* Stephen G. Kunin & Andrew K. Beverina, Commentary, KSR*'s Effect on Patent Law*, 106 Mich. L. Rev. First Impressions 50, 51 (2007), http://www.michiganlawreview.org/firstimpressions/vol106/kuninbeverina.pdf (summarizing the errors that the Supreme Court found in the Federal Circuit's nonobviousness jurisprudence).

149. *See* Lee Petherbridge & R. Polk Wagner, *The Federal Circuit and Patentability: An Empirical Assessment of the Law of Obviousness*, 85 Tex. L. Rev. 2051, 2103 (2007) (noting that, in deciding *KSR*, the Court was "reentering the area of obviousness after a hiatus of thirty-one years").

150. *See id.* at 2105 ("[I]n many ways, the Supreme Court's opinion in *KSR International* raises as many questions as it answers."); *see also The Supreme Court, 2006 Term—Leading Cases*, 121 Harv. L. Rev. 185, 385 (2007) ("The Court's decision in *KSR* did little to resolve outstanding patent law problems and left many questions unanswered.").

151. *See supra* Part I.B.2.c.

152. *See, e.g.*, Harold C. Wegner, Commentary, *Making Sense of* KSR *and Other Recent Patent Cases*, 106 Mich. L. Rev. First Impressions 39, 41 (2007), http://www.michiganlawreview.org/firstimpressions/vol106/wegner.pdf (arguing that the post-*KSR* "tightening of the patentability standard is . . . manifested by *KSR*'s endorsement of the 'obvious to try' standard that had been in disfavor throughout the history of the Federal Circuit").

153. *See* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007).

doing so, the Supreme Court addressed the obvious-to-try standard as follows:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.[154]

With this language, the Supreme Court conceivably advocated some version of an obvious-to-try standard of patentability.[155] Importantly, however, the Court limited this standard to scenarios accompanied by "predictable solutions" and "anticipated success."[156] Because the scope and meaning of these limitations likely will vary depending on the technological discipline in which they are invoked, the Supreme Court's indefinite obvious-to-try language arguably generated more questions than answers.[157]

While broad reaching in its review of obviousness jurisprudence, the facts in *KSR* related specifically to the mechanical arts.[158] On account of the compartmentalized nature of patent law,[159] however, the full impact of *KSR* in other technological and scientific disciplines remains unclear.[160] In

154. *Id.*

155. *See, e.g.*, Wegner, *supra* note 152, at 41.

156. *See KSR*, 127 S. Ct. at 1742.

157. *See, e.g.*, Jacqueline Benn, *Observations on Obviousness: Jackie Benn Reflects on the Impact of* KSR v. Teleflex, IP Persp., Winter 2008, at 8, 8, *available at* http://www.jonesday.com/pubs/pubs.aspx (search "Keyword" for "KSR"; then select hyperlink beginning with "*KSR v. Teleflex*: Moving Toward a More Flexible Definition of Obviousness . . .") ("*KSR* concerned the mechanical arts, which tend to be predictable, whereas the biotech arts have long been recognized by the Federal Circuit to be unpredictable."); James B. Lampert & Richard Goldenberg, *The Supreme Court Changes the Obviousness Standard: A First Look at* KSR, Email Alerts, (WilmerHale, Boston, Mass.), May 4, 2007, http://www.wilmerhale.com/publications/whPubsDetail.aspx?publication=3674 ("One aspect of the Supreme Court's decision that will clearly engender future discussion is the role of 'obvious to try.' . . . But under what circumstances [does the Court's obvious-to-try language apply]? When anticipated success is likely, predictable, or only a fervent hope?"); Peter G. Thurlow & Gregory A. Castanias, KSR v. Teleflex*: The Supreme Court Rules That a Broader, More Flexible Standard for Obviousness Is Consistent with Section 103 and Supreme Court Precedent*, Jones Day Commentaries (Jones Day, New York, N.Y.), May 2007, http://www.jonesday.com/pubs/pubs_detail.aspx?pubID=S4196 (describing *KSR*'s "new standards" for obviousness, including "obvious to try," and questioning "whether a single, articulable standard for obviousness will emerge from the Federal Circuit as it applies the *KSR* decision").

158. *See generally KSR*, 127 S. Ct. 1727.

159. *See, e.g.*, Burk & Lemley, *Technology-Specific*, *supra* note 47, at 1183–85.

160. Early commentary provides some insight into the possible impact of *KSR* in different areas of technology. *See, e.g.*, Matthew J. Dowd et al., KSR International Co. v. Teleflex Inc.*: Another Small Issue for Nanotechnology?*, 4 Nanotechnology L. & Bus. 293, 304 (2007) (arguing that *KSR* will likely increase the time and cost associated with obtaining a patent on a nanotechnology invention and will create more uncertainty as to whether nanotechnology patents will be obtainable); Benn, *supra* note 157, at 4 (noting the different

particular, the question of how an arguably retooled obvious-to-try standard might impact the pharmaceutical and biotechnology industries is an open question—indeed, several court decisions confirm an as yet unsettled approach to obviousness analysis in this context.[161]

II. POST-*KSR* INTERPRETATIONS OF THE "OBVIOUS TO TRY" PATENTABILITY STANDARD

KSR cast doubt on the impropriety of the obvious-to-try standard.[162] Specifically, as discussed below, several post-*KSR* decisions illustrate the present uncertainty regarding its correct application to inventions in the pharmaceutical arts.

A. Pfizer v. Apotex*: A Proper Role for "Obvious to Try"?*

A patent dispute over a blockbuster hypertension drug offered an initial glimpse into how the Federal Circuit might interpret obviousness, including the obvious-to-try question, following *KSR*.[163] The case pertained to the marketed salt form[164] of amlodipine, the active ingredient in Norvasc, the

degrees of predictability characteristic of the mechanical and biotechnological arts, and concluding that "the extent to which the Court of Appeals for the Federal Circuit will find *KSR* applicable to the biotech arts is uncertain"); Courtenay C. Brinckerhoff, KSR*: A Bump in the Road for Biotech?*, Genetic Engineering & Biotechnology News, July 1, 2007, http://www.genengnews.com/articles/chitem.aspx?aid=2150 (noting that *KSR* "is not cause for alarm in the biotech industry" and "may not have as much of an impact on the biotech industry as it will on other fields"); Greenhouse, *supra* note 17 (quoting patent lawyer Cynthia Kernick as stating, "'Nearly every patent that contains a combination of prior ideas is at risk because [*KSR*] has dramatically broadened the standard of obviousness'"); Barry L. Grossman, KSR v. Teleflex—*Are Medical Device Patents at Risk?*, Pulse (Foley & Lardner LLP Chi., Ill.), Oct. 2007, at 5–6, *available at* http://www.foley.com/files/tbl_s31Publications/FileUpload137/4473/ThePulse_OCT_07.pdf (noting that, although the facts of *KSR* pertained to an automobile pedal, "the principles of the *KSR* case would apply equally as well" to patented medical devices; thus, *KSR* "is likely to make medical device patents harder to obtain and easier to invalidate"); Wegner, *supra* note 152, at 41 ("*KSR* impacts the validity determination of virtually *every* invention other than new entities of chemistry and biotechnology.").

161. *See infra* Part II.A–B; *cf.* Petherbridge & Wagner, *supra* note 149, at 2107 (predicting that, in general, *KSR* "may well muddy the waters of patentability for a time as the early obviousness cases work their way through the Federal Circuit").

162. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007) (discussing the obvious-to-try test).

163. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007). Although the Federal Circuit decided *Pfizer* prior to *KSR*, the court considered the combined petition for panel rehearing and rehearing en banc following *KSR*. *See infra* notes 186–88 and accompanying text.

164. A "salt," in a chemical sense, is the product of an acid-base reaction; in a "pharmaceutical salt," either the acid or the base is a drug compound. Salt formation is a common practice in the pharmaceutical industry. *See, e.g.*, Camille G. Wermuth & P. Heinrich Stahl, *Introduction* to Handbook of Pharmaceutical Salts: Properties, Selection and Use 1 (P. Heinrich Stahl & Camille G. Wermuth eds., 2002) ("An estimated half of all the drug molecules used in medicinal therapy are administered as salts, and salification of a drug substance has become an essential step in drug development.").

world's largest-selling hypertension drug.[165] Pfizer originally developed amlodipine as a maleate salt,[166] but encountered two problems: chemical instability and a tendency of the tablet blend to stick to manufacturing equipment.[167] To overcome these drawbacks, Pfizer searched for an alternative salt form of amlodipine and eventually switched to the besylate salt, which possessed improved stability and nonstickiness over amlodipine maleate.[168] At issue in *Pfizer* was the validity of claims directed to amlodipine besylate in light of prior art, including, inter alia, the patent that originally disclosed the amlodipine maleate salt and a publication that described fifty-three different salt-forming acids previously approved for use in various marketed pharmaceuticals.[169] Reversing a district court decision, the Federal Circuit panel found that claims directed to the amlodipine besylate salt were invalid as obvious.[170]

The obviousness determination in *Pfizer* is noteworthy in several respects. The court explicitly refrained from equating unpredictability with nonobviousness. Citing to, inter alia, *In re Merck & Co.* and *In re O'Farrell*,[171] the Federal Circuit found clear error in the district court's conclusion that, since "it was generally unpredictable as to whether a particular salt would form and what its exact properties would be," it follows that a "skilled artisan would have had no expectation of success in making a besylate salt of amlodipine."[172] Thus, notwithstanding the district court's findings that a skilled artisan could not predict whether any particular salt would form, and, moreover, whether any salt that did form would possess desirable properties,[173] the Federal Circuit held that even this degree of unpredictability cannot confer nonobviousness.[174]

In finding the claimed invention obvious, the Federal Circuit replaced the district court's finding—that, in attempting to synthesize amlodipine besylate, a skilled artisan would not have possessed a reasonable expectation of success—with its own determination that an expectation of success would have existed.[175] In so doing, however, the Federal Circuit

165. *See* Petition for a Writ of Certiorari at 2, *Pfizer*, 480 F.3d 1348 (No. 2006-1582), 2007 WL 1573945 ("Amlodipine besylate is the active ingredient in Norvasc®, which is the world's largest selling brand-name drug for treating hypertension.").

166. *See Pfizer*, 480 F.3d at 1353 (noting that amlodipine maleate salt is the product of the acid-base reaction between amlodipine (a base) and maleic acid).

167. *See id.*

168. *See id.* (noting that amlodipine besylate is the acid-base reaction product of amlodipine and benzene sulphonic acid).

169. *See id.* at 1355–57.

170. *See id.* at 1372.

171. *See supra* notes 108–10, 139–43 and accompanying text.

172. *Pfizer*, 480 F.3d at 1364 ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

173. *See id.* at 1364 ("We cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be.").

174. *See id.*

175. *See id.* at 1364–65.

inferred an expectation of success from the inventor's own beliefs, rather than from the perspective of the ordinary skilled artisan.[176]

Casting aside the requirement of objectivity can significantly elevate the standard for patentability, as *Pfizer* illustrates. By conducting the experiment leading to the putative invention, the inventor must have possessed a subjective expectation of success; otherwise, he would not have reasonably expended the time and effort involved in experimentation.[177] If the inventor's own expectations were the proper yardstick by which to measure patentability, nonobvious inventions could result only from unreasonable experimentation or serendipitous discoveries,[178] not the rational, premeditated approach that characterizes pharmaceutical research and development.[179]

Pfizer had argued that because there existed no reasonable expectation of success, the besylate salt of amlodipine was, if anything, merely "obvious to try" and therefore patentable.[180] But the Federal Circuit disagreed, stating that an amlodipine besylate salt was "not merely obvious to try . . . but would have been indeed obvious to make"[181]—despite conceding that salt formation is unpredictable,[182] and despite undisputed testimony that the advantageous properties of amlodipine besylate could not have been predicted.[183] By viewing amlodipine besylate's obviousness from the subjective viewpoint of its inventor, the court departed from the requirement that obviousness be judged objectively, thereby eschewing the objective "reasonable expectation of success" requirement. In so doing, the *Pfizer* court effectively embraced the obvious-to-try standard of

176. *See id.* at 1364 (holding that "[t]he evidence would convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success" by referring to the inventor's own testimony about his personal expectations and beliefs).

177. *See* Corrected Brief Amici Curiae of SmithKline Beecham Corp. (d/b/a GlaxoSmithKline) and Eli Lilly and Co. in Support of Petitioner Pfizer Inc. at 5, *Pfizer*, 480 F.3d 1348 (No. 06-1261), 2007 WL 1171048 [hereinafter SKB Brief].

178. *See In re* Lindell, 385 F.2d 453, 455 (C.C.P.A. 1967) ("Serendipity is not a prerequisite to patentability.").

179. *See* SKB Brief, *supra* note 177, at 9.

180. *Pfizer*, 480 F.3d at 1365 ("Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be 'obvious to try,' i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained.").

181. *Id.* at 1366.

182. *See id.* at 1364–66 (conceding that "we recognize some degree of unpredictability of salt formation" and that "[w]e cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be").

183. *See* Petition of Plaintiff-Appellee Pfizer Inc. for Rehearing and Rehearing En Banc at 5–8, 15–17, Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377 (Fed. Cir. 2007) (No. 2006-1261), 2007 WL 1175774 (arguing that "[t]he undisputed testimony . . . was that the properties of a new salt are entirely unpredictable"). Pfizer also argued that the beneficial properties of amlodipine besylate constituted unexpected results that rebutted any prima facie obviousness, but the court viewed these properties as nothing more than the result of "routine optimization." *Pfizer*, 480 F.3d at 1371–72 ("[E]ven if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case.").

patentability,[184] despite simultaneously proclaiming that "'obvious to try' is not the proper standard by which to evaluate obviousness."[185]

1. Denial of Rehearing

The Federal Circuit decided *Pfizer* prior to, and thus without the perspective of, the Supreme Court's pronouncement on obviousness in *KSR*, discussed above.[186] But because the Federal Circuit considered Pfizer's petition for rehearing and rehearing en banc following the *KSR* decision, *Pfizer* nevertheless afforded the court an opportunity to reconsider its holding in light of *KSR*.[187] By denying Pfizer's petition for rehearing en banc, a majority of the Federal Circuit essentially indicated that *Pfizer* accorded with the Supreme Court's holding in *KSR*.[188]

Although the Federal Circuit denied Pfizer's petition for rehearing,[189] three judges, in separate dissenting opinions, maintained that the panel's decision warranted en banc review.[190] Among the various rationales for rehearing advanced in the three dissenting opinions, Judge Pauline Newman's dissent asserted that the Federal Circuit panel improperly applied "the obvious-to-try standard [] in direct conflict with precedent."[191]

184. *See* Kunin & Beverina, *supra* note 148, at 52. The authors refer to *Pfizer* as a "heavily criticized" decision, but one that is "not necessarily inconsistent with KSR." *Id.* They state that the criticism of *Pfizer* has been that it misapplies, not ignores, the reasonable expectation of success doctrine. *Id.*

185. *Pfizer*, 480 F.3d at 1365.

186. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007) (decided Apr. 30, 2007); *Pfizer*, 480 F.3d 1348 (decided Mar. 22, 2007).

187. Petition of Plaintiff-Appellee Pfizer Inc. for Rehearing and Rehearing En Banc, *supra* note 183, at 5–8, 15–17.

188. *See* Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377, 1378 (Fed. Cir. 2007). The Federal Circuit denied rehearing in *Pfizer* on May 21, 2007, three weeks after the Supreme Court decided *KSR*. *See id.* at 1377. However, as indicated in Pfizer's reply brief in support of certiorari, the fact that the Federal Circuit issued its denial of rehearing in *Pfizer* after the Supreme Court's decision in *KSR* may not warrant a presumption that the Federal Circuit actually considered *KSR*. *See* Reply for Petitioner at 1–3, *Pfizer*, 480 F.3d 1348 (No. 2006-1582), 2007 WL 2010142. In *Lord's Landing Village Condominium Council of Unit Owners v. Continental Insurance Co.*, 520 U.S. 893 (1997), an intervening state court decision called into question a federal appellate court's holding in a diversity case, and the Supreme Court considered whether to grant a petition for certiorari, vacate the federal appellate court's judgment, and remand the case (GVR) to the lower court for further consideration of the state court decision. *See id.* at 894. In *Lord's Landing*, the intervening decision was expressly, albeit "ambiguous[ly]," addressed by the lower court in its denial of a motion to stay or recall its mandate. *See id.* at 896–97. The Supreme Court nevertheless issued a grant, vacate, and remand order, holding that the lower court's "ambiguous statement . . . does not establish that it actually considered and rejected" arguments based on the intervening state court decision. *Id.* By comparison, in the *Pfizer* denial of rehearing, the majority did not reference or discuss the intervening *KSR* decision; only Judge Alan D. Lourie's dissenting opinion acknowledged *KSR*. *Pfizer*, 488 F.3d at 1383.

189. *Pfizer*, 488 F.3d at 1378.

190. *Id.* at 1379–84 (Newman, Lourie & Rader, JJ., dissenting from the court's denial of rehearing en banc).

191. *Id.* at 1379 (Newman, J., dissenting).

Citing to *In re Tomlinson*, discussed above,[192] Judge Newman acknowledged that "'there is usually an element of "obviousness to try" in any research endeavor,'"[193] and she continued by noting the impropriety of the obvious-to-try standard, particularly with respect to the "methodical research" characteristic of the pharmaceutical and biotechnology industries, "where small change can produce large differences."[194]

Similarly, Judge Randall R. Rader noted that "'obvious to try' jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis."[195] He chastised the panel for giving "lip service" to the notion that "'obvious to try' does not work in [the pharmaceutical] field" while nonetheless basing its decision on this improper standard.[196]

2. *Pfizer*'s Application to Subsequent Cases

Although decided by the Federal Circuit only recently, the court has followed *Pfizer* in two relevant opinions. In *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*,[197] a case involving the blood pressure medication Altace, the Federal Circuit overturned a "close" district court ruling[198] of nonobviousness. The obviousness allegation specifically centered on claims to a pharmaceutical composition that was "a purified form of a mixture that existed in the prior art."[199] The Federal Circuit arrived at a prima facie case of obviousness by, in essence, finding that a skilled artisan would have possessed a reasonable expectation of success.[200] The Federal

192. *In re* Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966); *see supra* notes 127–31 and accompanying text.

193. *Pfizer*, 488 F.3d at 1379 (Newman, J., dissenting) (quoting *Tomlinson*, 363 F.2d at 931).

194. *See id.* at 1379 (referencing amici curiae briefs representing research pharmaceutical industries, which point out that "methodical experimentation is fundamental to scientific advance, and particularly for biological and medicinal products, where small change can produce large differences").

195. *Id.* at 1384 (Rader, J., dissenting) ("[S]alt selection is unpredictable, thus rebutting . . . any reasonable expectation of success.").

196. *See id.*

197. *See* 499 F.3d 1293 (Fed. Cir. 2007).

198. Aventis Pharma Deutschland GmbH v. Lupin, Ltd., No. 2:05cv421, 2006 U.S. Dist. LEXIS 48246, at *129–30 (E.D. Va. July 17, 2006), *rev'd*, 499 F.3d 1293 (Fed. Cir. 2007) ("Although it is very a close question [sic] . . . the Court finds that a person of ordinary skill in the art would not by clear and convincing evidence have necessarily been motivated to isolate [the claimed composition]." (emphasis omitted)).

199. *See Aventis*, 499 F.3d at 1301.

200. *See id.* at 1302 ("Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art."). The Federal Circuit and the CCPA have also taken an opposite view toward the separation of enantiomers from a racemic pharmaceutical compound. *See, e.g.*, Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007), *reh'g denied*, No. 2007-1059, 2007 U.S. App. LEXIS 26974 (Fed. Cir. Oct. 12, 2007) (affirming the nonobviousness of a single enantiomer antidepressant drug in light of a prior

Circuit overturned the district court's finding in this regard.[201] Citing *Pfizer*'s holding that "there was an insufficient showing that the properties of amlodipine besylate . . . were unexpectedly superior to other obvious-to-try salts,"[202] the *Aventis* court appeared to follow *Pfizer* to the extent that *Pfizer* discounted the district court's factual finding of no reasonable expectation of success and justified an obviousness holding on the obvious-to-try rationale.

Another decision involving a "close question" of obviousness, *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, also supported prima facie obviousness by citing to, inter alia, *Pfizer*.[203] In *PharmaStem*, the claimed inventions involved compositions and methods relating to a medical procedure for treating persons with compromised blood and immune systems by isolating stem cells from umbilical cord blood.[204] With respect to the validity of the two patents at issue, a jury had returned a verdict of nonobviousness.[205] Defendants ViaCell et al. appealed the district court's refusal to grant their motion for judgment as a matter of law with regard to invalidity of the two patents.[206]

Concluding that a reasonable jury could not have found the invention nonobvious, the Federal Circuit reversed the district court's denial of the motion for judgment of invalidity as a matter of law.[207] Citing *Pfizer* for the proposition that "the expectation of success need only be reasonable, not absolute,"[208] the *PharmaStem* court found, in contrast to the jury, that evidence showed that a reasonable researcher would have possessed an expectation of success.[209] As in *Aventis*, it appears that the *PharmaStem* court used *Pfizer* to derail evidence that a skilled artisan would have lacked any reasonable expectation of success.

art racemate, where the district court found that a skilled artisan would have had no reasonable expectation of success in attempting to separate the enantiomers); *In re* May, 574 F.2d 1082, 1094 (C.C.P.A. 1978) ("[The] actual unexpected difference in properties between the claimed compound and its isomers" negated prima facie obviousness.).

201. *See Aventis*, 2006 U.S. Dist. LEXIS at *132–33 ("[T]here was no expectation that [the claimed compound] would be more or less potent than a mixture.").

202. *See Aventis*, 499 F.3d at 1302–03 (citing Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368–69 (Fed. Cir. 2007)).

203. PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1359, 1364 (Fed. Cir. 2007), *cert. denied*, 2008 WL 102402 (U.S. 2008).

204. *See id.* at 1347.

205. *See id.* at 1346–47.

206. *See id.* at 1347.

207. *See id.* at 1367.

208. *Id.* at 1364.

209. *See id.* at 1363 ("[T]he inventors merely used routine research methods to prove what was already believed to be the case."). The court also noted, "The evidence at trial demonstrated that the patentees did not invent a new procedure or a new composition; instead, they simply provided experimental proof that the [umbilical] cord blood could be used to effect hematopoietic reconstitution of mice and, by extrapolation, could be expected to work in humans as well." *Id.* at 1364–65 (citing *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Judge Newman, in dissent, noted as much. She criticized the majority for brushing aside the trial court's finding of no reasonable expectation of success[210] and for grounding its own obviousness holding on a finding "that 'a person of ordinary skill in the art would have had reason to attempt to make [the claimed inventions].'"[211] She continued by pointing out the pitfalls associated with the majority's obvious-to-try analysis: "My colleagues go too far in limiting the patent system to the serendipitous and the unexpected. . . . Scientific methodology usually starts with a hypothesis based on what is already known . . . ."[212]

At the very least, *Aventis* and *Pharmastem* illustrate the Federal Circuit's post-*Pfizer* inclination to reach an obviousness holding by disparaging evidence below that a skilled artisan would not have possessed a reasonable expectation of success. Based on these cases alone, however, it is less clear whether the court has wholeheartedly embraced the obvious-to-try standard, in effect spurning any substantive consideration of objective expectations, or whether the court has instead simply elevated the bar as to the evidence required to prove an absence of such an expectation of success.

B. Takeda v. Alphapharm*: The Federal Circuit Revisits "Obvious to Try"*

Whereas the post-*KSR* rehearing denial in *Pfizer* and the subsequent holdings in *Aventis* and *Pharmastem* seemed to portend a revival of the obvious-to-try standard, the court took a contrary tack in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty*.[213] In *Takeda*, the court considered the validity of claims relating to the chemical structure of pioglitazone, the active ingredient in the blockbuster diabetes drug Actos.[214] Alphapharm, the company intending to market generic pioglitazone,[215] asserted that Takeda's claims were obvious in light of a prior art compound referred to as "compound b."[216] In essence, Alphapharm contended that the chemical differences between pioglitazone and compound b were such that

210. *Id.* at 1376 (Newman, J., dissenting) ("The record contains testimony that scientists working in the [relevant field] did not expect [umbilical] cord blood to be a successful transplant tissue or a useful source of hematopoietic stem cells [as required by the claims at issue]."). Referencing the testimony of PharmaStem's expert, Judge Pauline Newman noted that "persons of skill in this field would not have had a reasonable expectation of success in carrying out the claimed process." *Id.* at 1377.

211. *See id.* at 1377 (quoting *id.* at 1360 (majority opinion)).

212. *See id.* at 1378; *see also supra* note 178 and accompanying text.

213. 492 F.3d 1350 (Fed. Cir. 2007).

214. *See id.* at 1353. "Actos® has enjoyed substantial commercial success since its launch in 1999. By 2003 . . . gross sales for that year exceeded $1.7 billion." *Id.* at 1352–53.

215. *See Takeda*, 492 F.3d at 1354 (stating that Alphapharm filed a paragraph IV certification with its abbreviated new drug application pursuant to 21 U.S.C. § 505(j)(2)(B)(ii), asserting that the patent covering Takeda's product was invalid). A company indicates intent to market a generic product by filing an abbreviated new drug application, a mechanism under the Hatch-Waxman Act for obtaining FDA approval to manufacture and market a generic version of a previously approved drug. *See supra* note 29 and accompanying text.

216. *See Takeda*, 492 F.3d at 1355–56.

pioglitazone would have been obvious to one of ordinary skill at the time Takeda applied for its patent.[217]

The *Takeda* court, however, remained unconvinced. Affirming the district court's holding,[218] the Federal Circuit rejected Alphapharm's argument that compound b rendered pioglitazone obvious to try and therefore unpatentable in light of both *KSR* and *Pfizer*.[219] In doing so, the *Takeda* court focused on the Supreme Court's requirement in *KSR* that the claimed solution be "predictable" before it can be invalidated on obvious-to-try grounds.[220] Applying *KSR* to *Takeda*, the Federal Circuit pointed out that, "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."[221] The court thus emphasized the lack of predictability in the field of pharmaceutical chemistry in rejecting the obviousness attack on the active pharmaceutical ingredient in the Actos product.[222]

Alphapharm argued that *Pfizer* mandated a finding of obviousness, but the court distinguished *Pfizer* on its "'particularized facts.'"[223] According to the court, whereas in *Pfizer* there was "'ample motivation to narrow the genus'" to a few possible solutions, including the claimed invention, in *Takeda* there was "nothing in the prior art to narrow the possibilities of a lead compound to compound b," and one of ordinary skill would have avoided compound b based on its "identified adverse effects."[224] The court thus concluded that Alphapharm failed to establish a prima facie case of obviousness.[225]

The court then carried its obviousness analysis a step further. Assuming, despite its finding to the contrary, that the prior art would have led to the selection of compound b as a "lead compound" for further diabetes

217. *See id.*

218. The *Takeda* court noted that in cases involving a new chemical compound, a prima facie case of obviousness requires (1) structural similarity, plus (2) "some reason that would have led a chemist to modify a known compound in a particular manner" to produce the claimed compound. *See id.* at 1356–57. A reason to modify compound b to make pioglitazone, the court held, was absent from the prior art; thus, Alphapharm failed to establish obviousness. *See id.*

219. *See id.* at 1359 ("We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, [*Pfizer*], mandates reversal." (citation omitted)).

220. KSR Int'l. Co. v. Teleflex Inc., 127 S. Ct. 1727, 1732 (2007).

221. *Takeda*, 492 F.3d at 1359.

222. *See id.* at 1359 ("Thus, this case fails to present the type of situation contemplated by the [Supreme] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.' The evidence showed that it was not obvious to try.").

223. *See id.*

224. *See id.* at 1359–60 (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1363 (Fed. Cir. 2007)). The Federal Circuit credited the district court's factual findings that in terms of toxicity and activity "compound b was not identified as one of the three most favorable compounds" in the prior art; that the prior art, in describing certain negative biological effects associated with compound b, "taught away from compound b"; and that "any suggestion to select compound b was essentially negated by the disclosure of the [prior art] reference." *Id.* at 1358.

225. *See id.* at 1358–60.

research, the *Takeda* court considered whether a skilled artisan would have had a reasonable expectation of success that chemically modifying compound b would have resulted in beneficial changes in toxicity or efficacy.[226] Two discrete chemical modifications, termed "homologation" and "ring-walking," were necessary to convert compound b into pioglitazone, and the *Takeda* court affirmed the district court's findings that neither chemical modification would have been accompanied by a reasonable expectation of success.[227]

Put differently, the court held that even if pioglitazone were obvious to try based upon the prior art disclosure of compound b, the prior art demonstrated that a skilled chemist would not have possessed a reasonable expectation of success that performing the particular chemical modifications would result in a compound with beneficial antidiabetic properties.[228] The court concluded that Alphapharm "failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds."[229]

The apparent tension between the Federal Circuit's juxtaposed holdings in *Pfizer* and *Takeda* embodies the court's unsettled approach toward interpreting *KSR*'s "obvious to try" language. Whether the court will eventually realign itself with the post–Patent Act aversion to the obvious-to-try test[230] (as indicated by *Takeda*), or whether it will revert to the pre–Patent Act acceptance of applying the obvious-to-try rationale,[231] even in the unpredictable pharmaceutical arts (as suggested by *Pfizer*), remains an open question.

C. *The PTO Interprets "Obvious to Try"*

Notwithstanding the Federal Circuit's apparent ambiguity regarding *KSR*'s obvious-to-try test, the PTO set forth its own interpretation of *KSR* in its obviousness examination guidelines.[232] In response to *KSR*, the

226. *See id.* at 1360–61.

227. *See id.* at 1360–62 ("With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. . . . As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions . . . on a pyridyl ring would result in beneficial changes. . . . The court's characterization of pioglitazone's unexpected results is not clearly erroneous.").

228. *See id.*

229. *See id.* at 1363.

230. *See supra* Part I.B.2.

231. *See supra* Part I.B.1.

232. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,526, 57,526 (Oct. 10, 2007) [hereinafter PTO Obviousness Guidelines] (noting that "[t]hese guidelines do not constitute substantive rule making and hence do not have the force and effect of law"); *see also id.* at 57,532–33. The guidelines were subsequently incorporated into the Manual of Patent Examining Procedure. *See* MPEP, *supra* note 10, § 2143.

guidelines listed "Obvious to Try" among seven separate rationales for supporting obviousness rejections in the examination of patent applications.[233] According to the guidelines, before basing a claim rejection on the obvious-to-try rationale, a patent examiner must make four factual findings[234]: (1) identification of a recognized problem or need, (2) "a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem," (3) the existence of a "reasonable expectation of success" in pursuing the known potential solutions, and (4) any relevant factual inquiries required under *Graham v. John Deere Co*.[235]

The PTO guidelines referenced three opinions—two Federal Circuit cases, *Pfizer*[236] and *Alza Corp. v. Mylan Laboratories, Inc.*,[237] and one precedential opinion of the Patent Board, *Ex parte Kubin*[238]—to "illustrat[e] how [the obvious-to-try rationale] may be used to support a finding of obviousness."[239] Of these three opinions, however, only *Kubin* actually discussed *KSR*.[240] In *Kubin*, a biotechnology case,[241] the Patent Board affirmed an obviousness rejection of a claimed nucleic acid molecule.[242] Discussing the rationale behind its obviousness holding, the Patent Board remarked that, "[u]nder *KSR*, it's now apparent 'obvious to try' may be an appropriate test in more situations than we previously contemplated."[243] The Patent Board further noted that "there were a limited number of methodologies available" to isolate the claimed compound, and "[t]he

233. *See* PTO Obviousness Guidelines, *supra* note 232, at 57,528–29. The guidelines "[n]ote that the list of rationales . . . is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel." *Id.* at 57,528.

234. The findings must be made as of the time the application was filed; moreover, "[i]f any of these findings cannot be made, then [the obvious-to-try] rationale cannot be used to support a conclusion [of obviousness under § 103]." *See id.* at 57,532.

235. *See id. Graham* is discussed in more detail at *supra* notes 39–46 and accompanying text.

236. *See supra* Part II.A.

237. 464 F.3d 1286 (Fed. Cir. 2006). In *Alza*, the Federal Circuit affirmed the obviousness of a sustained-release oral formulation of a previously approved urinary incontinence drug. *See id.* at 1288–89. In doing so, the court affirmed the district court's finding that "'a person of ordinary skill . . . [would have had] a reasonable expectation of success of producing a [sustained release] formulation meeting the [disputed] claims . . . .'" *Id.* at 1293–94 (quoting Alza Corp. v. Mylan Labs., Inc., 388 F. Supp. 2d 717, 740 (N.D. W. Va. 2005)).

238. 83 U.S.P.Q.2d (BNA) 1410 (B.P.A.I. 2007).

239. *See* PTO Obviousness Guidelines, *supra* note 232, at 57,529, 57,532–33.

240. The Federal Circuit decided both *Alza* and *Pfizer* prior to *KSR*, although the court denied Pfizer's petition for rehearing after *KSR*. *See Pfizer*, 480 F.3d 1348 (Fed. Cir. 2007) (decided Mar. 22, 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007) (decided May 21, 2007); *Alza*, 464 F.3d 1286 (decided Sept. 6, 2006). *See also* sources cited *supra* note 186.

241. The claimed invention in *Kubin* involved polynucleotides, which encode polypeptides that form part of the body's innate immune system. *See Kubin*, 83 U.S.P.Q.2d at 1411.

242. *See id.* at 1413–15.

243. *Id.* at 1414.

skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful."[244]

Whether or not *Kubin*, by distinguishing the landmark nonobviousness case of *In re Deuel*,[245] represented a post-*KSR* adjustment of patentability in the biotechnology field,[246] its obviousness analysis is not procedurally pioneering in a general sense. Although the Patent Board recited *KSR*'s "obvious to try" language, it did not, as *KSR* requires,[247] analyze predictability in the context of its obviousness determination.[248] Instead, a clear basis for its holding involved the finding of a "reasonable expectation" of success.[249] Thus, if *Kubin* illustrated the application of a new § 103 "obvious to try" rationale, as the PTO suggested, it would appear to be "obvious to try" in name only.

In setting forth its obvious-to-try examination guidelines, the PTO enmeshed *Pfizer*,[250] a pharmaceutical case in which the Federal Circuit arguably advocated ignoring the absence of any reasonable expectation of success, with *Kubin*,[251] a biotechnology case in which the Patent Board specifically based its holding on the existence of such an expectation of success.[252] The result of this tangled jurisprudence adds little clarity to the broader issue of the propriety of the obvious-to-try test in the biotechnology and pharmaceutical arts, and prospective patentees will certainly benefit from additional clarification from the Federal Circuit.

D. Sanofi v. Apotex*: A Litmus Test*

A case currently on appeal before the Federal Circuit may dispel some of the ambiguity surrounding the obvious-to-try inquiry in the pharmaceutical arts.[253] *Sanofi-Synthelabo v. Apotex, Inc.* involves a validity challenge to a

244. *Id.*

245. *See id.* at 1413 ("Regardless of some factual similarities between *Deuel* and this case, *Deuel* is not controlling and thus does not stand in the way of our conclusion . . . ."). See *supra* notes 145–46 and accompanying text for discussion of *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

246. *See, e.g.*, Posting of Kevin E. Noonan to Patent Docs: Biotech & Pharma Patent Law & News Blog, http://www.patentdocs.net/patent_docs/2007/07/ex-parte-kubin-.html (July 18, 2007, 11:05 AM) (arguing that *Kubin* misapplied *KSR* and mistakenly "conflate[d] the obviousness of a method for isolating a cDNA with obviousness of the cDNA isolated").

247. *See supra* notes 154–56 and accompanying text.

248. In the context of determining whether the claims were enabled, as required by 35 U.S.C. § 112, the Patent Board found "that molecular biology is generally an unpredictable art (and thus was so at the time the application was filed)." *Kubin*, 83 U.S.P.Q.2d at 1416.

249. *See id.* at 1413–15.

250. *See supra* Part II.A.

251. *See supra* notes 241–49 and accompanying text.

252. The PTO also referenced the pre-*KSR* case of *Alza*, discussed *supra* note 237. While not explicitly addressing the obvious-to-try test, *Alza*'s obviousness holding centered on the district court's finding of a reasonable expectation of success, thus apparently conforming to the established view of obviousness in the pharmaceutical arts. *See* Alza Corp. v. Mylan Laboratories, Inc., 464 F.3d 1286, 1295.

253. *See* Sanofi-Synthelabo v. Apotex Inc., 492 F. Supp. 2d 353 (S.D.N.Y. 2007), *appeal docketed*, No. 2007-1438 (Fed. Cir. Sept. 4, 2007).

patent covering the active ingredient in Plavix, a commercially successful antiplatelet drug prescribed to patients at risk of heart attack and stroke.[254] A primary issue in *Sanofi* is the obviousness of clopidogrel bisulfate, which, as a pharmaceutical salt, bears some relationship to the active ingredient at the center of the *Pfizer* Norvasc case.[255]

The district court opinion details the prolonged development history of clopidogrel bisulfate.[256] In essence, the progression to clopidogrel bisulfate from its development pipeline predecessor, a chemical substance termed "PCR 4099," involved two principal steps.[257] The first step involved the separation of PCR 4099 into its two component forms.[258] Akin to the case of thalidomide, discussed above,[259] one of the forms of PCR 4099 possessed all of the beneficial antiplatelet activity, whereas the other was "completely ineffective,"[260] "more toxic," and specifically responsible for certain known side effects.[261] The beneficial component of PCR 4099 is the compound called clopidogrel.[262]

Once Sanofi researchers isolated clopidogrel from PCR 4099, the second principal step in developing Plavix was the synthesis of a salt form suitable for use in commercial tablets.[263] Upon experimenting with more than twenty different acids, the researchers discovered clopidogrel bisulfate, which "proved to be the only salt with the optimal properties."[264]

Apotex, the patent infringer,[265] challenged the validity of Sanofi's patent before the U.S. District Court for the Southern District of New York by alleging, inter alia, that the claim to clopidogrel bisulfate was obvious over an earlier Sanofi patent disclosing a broad genus of compounds including PCR 4099.[266] Apotex alleged that, based on the disclosure of PCR 4099, it would have been obvious for a person of ordinary skill to isolate clopidogrel and then make the bisulfate salt.[267] With respect to the salt

254. Plaintiffs-Appellees' Brief at 3, Sanofi-Synthelabo v. Apotex, Inc., No. 2007-1438 (Fed. Cir. Oct. 25, 2007), 2007 WL 3338903 (noting that in 2005 Plavix had U.S. sales of approximately $3.2 billion and was the second-largest-selling drug worldwide).

255. *See* Sanofi, 492 F. Supp. 2d at 373–76. Like any salt, clopidogrel bisulfate is the product of an acid-base reaction: clopidogrel (a base) reacts with sulfuric acid to yield clopidogrel bisulfate. *Id.*; *see also supra* note 164.

256. *See Sanofi*, 492 F. Supp. 2d at 358–81.

257. *See id.* at 366–79.

258. PCR 4099 is chemically termed a "racemate," and its two component forms are "enantiomers." *See id.* at 359, 371–73. *See generally Darrow*, *supra* note 2.

259. *See supra* notes 1–5 and accompanying text.

260. *See Sanofi*, 492 F. Supp. 2d at 376.

261. *See id.* at 378.

262. *Id.* at 376.

263. *Id.* at 373–76.

264. *Id.* at 375 (noting that the clopidogrel bisulfate salt alone possessed "a high melting point, long-term stability, non-hygroscopicity, and good solubility").

265. The parties stipulated that Apotex's generic product infringed Sanofi's patent covering clopidogrel bisulfate. *Id.* at 381.

266. *Id.* at 389. The broad genus disclosed clopidogrel (but not its sulfate salt) as one of "millions of possible compounds." *Id.* at 384. Apotex also unsuccessfully argued that clopidogrel bisulfate was inherently anticipated by this genus disclosure. *Id.* at 382–88.

267. *Id.* at 389.

formation, the obviousness argument paralleled that in *Pfizer*[268]: in essence, Apotex contended that it would have been obvious to try to make clopidogrel bisulfate based on information available in the prior art.[269]

The Federal Circuit issued its opinion in *Pfizer*[270] three months prior to the *Sanofi* decision.[271] Due to the similar factual underpinnings of *Pfizer* and *Sanofi*, the district court had to address squarely the *Pfizer* holding. In doing so, the district court held that *Pfizer*'s facts were distinguishable from those in *Sanofi*.[272] The court noted that "it is not enough for Apotex to have shown that the [claimed clopidogrel bisulfate] would have been 'obvious to try.'"[273] Whereas the "Pfizer chemists had identified the besylate salt as an option that they expected to succeed,"[274] the *Sanofi* court found that no analogous expectation of success existed with the bisulfate salt of clopidogrel.[275] The court concluded that the "unexpected success" of the bisulfate salt of clopidogrel independently supported its nonobviousness.[276]

The *Sanofi* appeal may cast an interesting shadow upon the Federal Circuit's holding in *Pfizer*. As discussed further in Part III,[277] the *Sanofi* appeal potentially presents the Federal Circuit with a choice between either upholding the nonobviousness of clopidogrel bisulfate, thereby adhering to the court's own long-standing employment of its expectation-of-success analysis, or following *Pfizer*, thereby adopting a post-*KSR* obvious-to-try approach even in the generally unpredictable pharmaceutical arts. Legal practitioners, scientific researchers and the public alike stand to benefit should the court seize upon the *Sanofi* appeal as an opportunity to clarify this muddled legal issue.

III. THE PROPER ROLE OF "OBVIOUS TO TRY" IN THE PHARMACEUTICAL ARTS

A. *The Enactment of § 103 Triggered the Subsequent Impropriety of the Obvious-to-Try Standard*

Prior to the enactment of 35 U.S.C. § 103, patentability determinations often invoked the indefinable "invention" requirement, ultimately with

268. *See* Pfizer, Inc. v. Apotex, Inc. 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007).
269. *See Sanofi*, 492 F. Supp. 2d at 389.
270. *Pfizer*, 480 F.3d at 1348 (decided Mar. 22, 2007).
271. *Sanofi*, 492 F. Supp. 2d at 353 (decided June 19, 2007).
272. *Id.* at 391 ("The Court . . . finds that *Pfizer* is distinguishable from this case. . . . *Pfizer* does not support the proposition that it would have been obvious to a person of ordinary skill in the art to formulate clopidogrel as a bisulfate salt.").
273. *Id.* at 388.
274. *Id.* at 391.
275. *See id.* at 391–92.
276. *See id.* at 392.
277. *See infra* Part III.E.

unsatisfactory results.[278] Indeed, dissatisfaction with this standard, together with a perceived hostility of courts toward patents,[279] prompted the statutory adoption in 1952 of "nonobvious subject matter" as a prerequisite to patentability.[280] Nevertheless, prior to the enactment of the nonobviousness requirement, certain court decisions rejecting patent validity relied upon a rationale akin to the modern obvious-to-try standard.[281] In *Mandel Bros.*, for example, the Supreme Court dismissed arguments that a skilled artisan would not have possessed any reasonable expectation of success, concluding instead that the artisan "would naturally and spontaneously have tried" to solve the identified problem using the claimed invention.[282] Prior to the 1952 Patent Act, therefore, an approach analogous to today's obvious-to-try test appears to have constituted an acceptable rationale for invalidating a claimed invention.[283]

It thus appears, perhaps counterintuitively, that the obvious-to-try test predates the statutory requirement of nonobviousness.[284] Regardless of the precise origins of "obvious to try," however, an analysis of court decisions following the 1952 Patent Act supports the view that the enactment of § 103 was a beachhead in establishing the impropriety of the obvious-to-try test.[285] Due in part to the Supreme Court's disinterest in patent cases during this period,[286] some time lapsed before courts fully embraced the consequences of § 103.[287] Nevertheless, in the decade following the enactment of § 103, courts moved gradually away from finding inventions unpatentable simply because it would have been obvious to follow a given research path.[288] The pace of retreat from "obvious to try" undoubtedly quickened following the influential Supreme Court opinion *Graham v. John*

278. *See supra* notes 97–99 and accompanying text. *See generally* Rich, *supra* note 103. Retrospectively contemplating the "invention" requirement, Judge Rich commented, "The requirement for 'invention' was at one and the same time a hard reality and a great mystery. Really, it was an absurdity." *Id.* at 30.

279. *See supra* notes 95–96 and accompanying text; *see also* Merges, *supra* note 103, at 2223 (noting that one purpose of the 1952 Patent Act was to overwrite a number of the Supreme Court's antipatent decisions from the period of 1930 to 1948, which Merges refers to as the Supreme Court's "most virulent anti-patent era").

280. *See supra* Part I.B.2.a.

281. *See supra* Part I.B.1.

282. *See* Mandel Bros. v. Wallace, 335 U.S. 291, 296 (1948).

283. *See supra* Part I.B.1.

284. *See* Merges, *supra* note 56, at 40 n.95 (noting that "[a]t one time 'obvious to try' was an accepted standard of obviousness" (citing *Mandel Bros.*, 335 U.S. at 295)). Note also that the statutory nonobviousness requirement itself developed from an earlier common law nonobviousness test set forth by the Supreme Court in *Hotchkiss*. *See* Dabney, *supra* note 101, at 132–35.

285. *See supra* Part I.B; *cf. In re* Huellmantel, 324 F.2d 998, 1001 n.3 (C.C.P.A. 1963) (stating that the obvious-to-try rationale "flies in the face of the plain language of the statute . . . [in which] [n]othing is said about 'obvious *to try*'").

286. *See* sources cited *supra* note 122.

287. *See* Rich, *supra* note 103, at 37 (noting the early reluctance of CCPA judges to abandon the "invention" requirement).

288. *See supra* Part I.B.2.b.

Deere Co., which stressed the importance of objectivity as a component of § 103's patentability analysis.[289]

B. *The Obvious-to-Try Test Directly Affects the Patentability of Pharmaceutical Inventions*

The post–Patent Act retreat from "obvious to try" as an indicator of patent validity[290] has particular relevance to the patentability of pharmaceutical inventions. One objective inquiry of importance to the pharmaceutical industry involves considering whether a person of ordinary skill in the art would have possessed a "reasonable expectation of success" upon following a particular course of research.[291] The importance of this inquiry relates to the high degree of unpredictability in the pharmaceutical arts—one may identify numerous interrelated variables with which to experiment, but without a reasonable expectation of success, the extensive resources[292] needed to pursue the ostensibly obvious-to-try research may not be economically justifiable.[293]

The obvious-to-try test, characterized by a finding of obviousness in the absence of a reasonable expectation of success, "specifically penalizes people in areas of endeavor where advances are won only by great effort and expense."[294] As such, the obvious-to-try test disproportionately impacts the pharmaceutical industry "because there is an overabundance of [chemically similar] structures that are obvious to try."[295] This is so, in part, because compounds that are substantially structurally similar can elicit drastically different biological responses, thus offering the potential for significant therapeutic advances.[296]

C. KSR*'s Discussion of the Obvious-to-Try Test Has Created Tension in the Federal Circuit, as Evidenced by* Pfizer *and* Takeda

KSR International Co. v. Teleflex Inc. stated that "obvious to try" is a valid patentability test in situations involving "a finite number of identified, predictable solutions."[297] In so stating, *KSR* apparently disrupted what had become a relatively uniform consensus regarding the test's impropriety.[298]

289. *See supra* Part I.B.2.c; *see also* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007) (reaffirming that *Graham* set forth an "objective" analysis for applying § 103 to assess a particular invention's patentability).

290. *See supra* notes 56–61 and accompanying text.

291. *See supra* notes 56–60 and accompanying text.

292. *See supra* note 59 (citing data indicating the high costs associated with pharmaceutical research and development).

293. *See, e.g.*, Merges, *supra* note 56, at 62 (arguing that the incentive for innovation is reduced in areas of research characterized by uncertainty and high cost).

294. *See In re* Merck & Co., 800 F.2d 1091, 1100 (Fed. Cir. 1986) (Baldwin, J., dissenting).

295. *See id.*

296. *See supra* notes 1–8 and accompanying text.

297. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007).

298. *See supra* Parts I.B.2.c, I.C.

Less clear is the issue of whether the Court, in advocating an obvious-to-try analysis without substantive discussion of its proper application, contemplated inventions beyond the realm of the mechanical arts. Certainly, the Court could have ameliorated much of the present uncertainty by delineating any subject-matter specificity imbued in its newly advanced obvious-to-try test. Instead, *KSR* leaves courts, patent examiners, and practitioners to wrangle with the fact that predictability undoubtedly varies by discipline.[299]

In the pharmaceutical arts, where research is characterized by substantial unpredictability,[300] an obviousness ruling has long required the consideration of whether a skilled artisan would have possessed a reasonable expectation of achieving a successful invention.[301] At least prior to *KSR*, this requirement signaled the impropriety of the obvious-to-try test, which dismisses substantive consideration of any expectation of success. But predictability, to some degree, is a consideration in any reasonable expectation of success analysis;[302] thus, a narrow reading of *KSR*'s "predictable solutions" terminology may support the view that the Court merely affirmed the Federal Circuit's obvious-to-try jurisprudence in the pharmaceutical arts. Because few pharmaceutical research results embody "predictable solutions" accompanied by "anticipated success," perhaps *KSR* suggested that the obvious-to-try patentability test is largely inappropriate in the pharmaceutical arts.

KSR's budding legacy in the Federal Circuit suggests that this interpretation may be oversimplified, however. Two post-*KSR* Federal Circuit decisions touching on the obvious-to-try issue, *Pfizer* and *Takeda*, illustrate seemingly divergent approaches toward the application of the obvious-to-try test in the pharmaceutical arts.[303]

In *Pfizer*, the Federal Circuit saw clear error in the district court's finding of no reasonable expectation of success, implicitly deeming the amlodipine besylate salt unpatentable as obvious to try.[304] Over the dissenting opinions of three judges, the court indicated, in effect, that *Pfizer* accorded with *KSR* by rejecting Pfizer's post-*KSR* petition for rehearing.[305] Indeed, the Federal Circuit has followed *Pfizer* in several subsequent, post-*KSR* opinions.[306]

In *Takeda*, on the other hand, the Federal Circuit distinguished *Pfizer* as controlling precedent and found that the active pharmaceutical ingredient pioglitazone would not have been obvious due to the unpredictability

299. *See, e.g.*, *infra* text accompanying note 328.
300. *See, e.g.*, *supra* note 59; *infra* note 323.
301. *See supra* notes 56–61 and accompanying text.
302. *See, e.g.*, *supra* note 57.
303. *See generally supra* Part II.A–B; *see also supra* Part II.A.1 (noting *Pfizer*'s post-*KSR* rehearing denial).
304. *See supra* text accompanying notes 180–85.
305. *See supra* Part II.A.1.
306. *See supra* Part II.A.2. The PTO has also relied on *Pfizer*'s holding in drafting its post-*KSR* obviousness examination guidelines. *See supra* Part II.C.

characteristic of the field of pharmaceutical chemistry.[307] Lacking evidence of predictability, the court could not find a reasonable expectation of success, and so declined to apply an obvious-to-try holding.[308] By contrast, the court in *Pfizer* acknowledged a similar degree of unpredictability, yet nevertheless divined the existence of a reasonable expectation of success.[309]

D. KSR*'s Obvious-to-Try Test Has Limited Applicability to the Pharmaceutical Arts*

What direction should the Federal Circuit take from this point forward? The fairest reading of the "predictable solutions" limitation to the obvious-to-try test discussed in *KSR*[310] acknowledges the milieu of the case—specifically, automobile accelerator pedals and, more generally, the mechanical arts.[311] Predictability upon combining mechanical elements does not comport with predictability—or, more accurately, the lack thereof—in performing molecular-scale alterations to pharmaceutical substances in the course of biomedical research. The addition of an electronic sensor to an adjustable mechanical pedal yielded no more than predictable results.[312] In striking contrast, the reaction of an active pharmaceutical ingredient with a second chemical substance to produce a third, chemically distinct entity—which may have the same or different therapeutic indication,[313] which may be more or less potent and/or toxic,[314] and which may possess physical properties deleterious or advantageous for its formulation, manufacture, storage, and/or administration[315]—epitomizes the act of research. The fruits of this empirical, tortuous process are not the "predictable solutions" and "anticipated success" envisioned within *KSR*'s mechanical arts framework.[316]

To the extent that *KSR* advocated readopting the forsaken[317] obvious-to-try test, one must bear in mind the subject-matter context of *KSR* in interpreting the meaning of its "predictable solutions" limitation.[318] In general, unlike the mechanical arts, innovation in the pharmaceutical industry results from substantial experimental research—for example, by making small chemical changes and measuring the resulting (oftentimes

307. *See supra* Part II.B.
308. *See supra* notes 218–22 and accompanying text.
309. *See supra* notes 172–74 and accompanying text.
310. *See supra* Part I.C.
311. *See, e.g.*, Dabney, *supra* note 101, at 144–47 (describing and depicting the claimed subject matter in the patent at issue in *KSR*).
312. *See* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").
313. *See supra* notes 6–8 and accompanying text.
314. *See supra* notes 3–5, 226–27, 258–62 and accompanying text.
315. *See supra* notes 166–68, 263–64 and accompanying text.
316. *KSR*, 127 S. Ct. at 1742; *see supra* Part I.C; *see also supra* note 59.
317. *See supra* Part I.B.2.b–c.
318. *See supra* text accompanying note 154.

substantial[319]) biological effects. Because mechanical-type predictability plays a relatively small role in pharmaceutical research, so too should *KSR*'s obvious-to-try test have limited applicability to obviousness determinations in the pharmaceutical arts. Unpredictability does not automatically confer patentability,[320] but it is an important and relevant consideration in determining whether a skilled artisan would have possessed a reasonable expectation of success in devising a particular research plan.[321]

E. *A Proper Reading of* KSR*'s Obvious-to-Try Test Supports the Patentability of the Claimed Invention in* Sanofi

Considerations such as the high degree of unpredictability in the pharmaceutical arts are paramount to forecasting the appropriate holding in the now-pending *Sanofi* appeal before the Federal Circuit.[322]

A central issue common to both *Pfizer* and *Sanofi* is the general unpredictability of whether a particular active pharmaceutical ingredient will form a salt, and whether any salt formed will ultimately possess desirable pharmaceutical properties.[323] In essence, *Pfizer* and *Sanofi* are at odds regarding the degree to which unpredictability may serve as a foundation for a finding of no reasonable expectation of success. As *Pfizer* illustrated, substantive disregard of unpredictability can lead to implicit adoption of the obvious-to-try test.[324] Were the Federal Circuit to follow *Pfizer* in the *Sanofi* appeal, as Apotex has urged,[325] *Sanofi* would likely be reversed.

319. *See supra* notes 1–8 and accompanying text.

320. *See* sources cited *supra* note 57.

321. *See, e.g.*, *supra* notes 57, 60.

322. *See supra* Part II.D.

323. *See* Pfizer, Inc. v. Apotex, Inc. 480 F.3d 1348, 1364 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007); *Sanofi*, 492 F. Supp. 2d at 374, 391–92. In fact, both *Pfizer* and *Sanofi* credited the same prior art reference regarding the state of the art of pharmaceutical salt formation. *See Pfizer*, 480 F.3d at 1355 (citing Stephen M. Berge et al., *Pharmaceutical Salts*, 66 J. Pharmaceutical Sci. 1 (1977)); *Sanofi*, 492 F. Supp. 2d at 373 (same). Relying on Berge et al., the *Sanofi* district court found that pharmaceutical salt formation involved a "high level of general unpredictability," and thus concluded that a skilled artisan "could not have reasonably expected that the bisulfate salt of clopidogrel would be the optimal pharmaceutical salt form of the compound." *Sanofi*, 492 F. Supp. 2d at 374–76. By contrast, in *Pfizer*, the Federal Circuit discounted the district court's finding that, "as Berge teaches and expert testimony on both sides accepted, '[t]here is no reliable way of predicting the influence of a particular salt species on the behavior of a parent compound'" to conclude that a "skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine." *Pfizer*, 480 F.3d at 1357, 1369 (quoting district court's bench order transcript).

324. *See* Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377, 1384 (Fed. Cir. 2007) (Rader, J., dissenting from denial of rehearing en banc) ("'[O]bvious to try' jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis.").

325. Brief for Defendants-Appellants at 60, *Sanofi*, No. 2007-1438, 2007 WL 2804161 ("This case is like *Pfizer* except the salts formed are much more obvious.").

On the other hand, it is unclear the extent to which the *Sanofi* district court considered the Supreme Court's *KSR* decision. As Apotex alleged in its appeal brief, "The district court legally erred in failing to apply *KSR*, which was decided months before the district court issued its decision but is never mentioned [in its opinion]."[326] Sanofi, in its reply brief, disputed this contention,[327] and further noted that, "[i]n any event, the facts of *KSR* are distant from this case. Unlike [the properties of] the mechanical invention in *KSR* . . . the properties of clopidogrel bisulfate . . . were highly unexpected."[328] Moreover, *Sanofi* did not benefit from *KSR*'s Federal Circuit progeny, including *Takeda*.[329] It therefore appears that, in deciding the *Sanofi* appeal, the Federal Circuit may choose either to emphasize *Pfizer*, which implicitly applied an obvious-to-try rationale by discounting evidence indicating no expectation of success,[330] or instead follow *Takeda*, which interpreted *KSR*'s holding in accordance with the unpredictable pharmaceutical arts.[331]

Applying *KSR* to *Sanofi* in a context-specific manner,[332] one must discern the predictability of (1) whether a particular acid-base combination will form a pharmaceutical salt, (2) the type of salt that may result, and (3) what properties any resulting salt would possess.[333] Indeed, both parties' experts, as well as the prior art, acknowledge that these elements "are all unpredictable."[334] Accordingly, this "high level of general unpredictability"[335] must be weighed together with the remarkable set of unexpected, beneficial properties accompanying the claimed clopidogrel bisulfate salt.[336]

As the court noted in *Takeda*, *KSR*'s obvious-to-try test is inappropriate for analyzing innovations in the pharmaceutical arts where—as in *Sanofi*—a skilled researcher could not have possessed a reasonable expectation of success on account of the numerous, interdependent, and unpredictable experimental variables.[337] Thus, in deciding *Sanofi*, the Federal Circuit should follow its approach in *Takeda*, which recognized the limitations

326. *Id.* at 42.

327. *See* Plaintiffs-Appellees' Brief, *supra* note 254, at 65 ("[T]he District Court . . . received supplemental briefing on *KSR* from the parties after it came down . . . .").

328. *Id.* at 66.

329. The Federal Circuit decided *Takeda* on June 28, 2007, about one week after Judge Sidney H. Stein of the Southern District of New York decided *Sanofi*.

330. *See supra* Part II.A.

331. *See supra* Part II.B; *see also* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350, 1359 (Fed. Cir. 2007) ("Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected . . . . Thus, this case fails to present the type of situation contemplated by the [Supreme] Court when it stated [in *KSR*] that an invention may be deemed obvious if it was 'obvious to try.'").

332. *See supra* Part III.D.

333. *See Sanofi*, 492 F. Supp. 2d at 374.

334. *See id.*

335. *Id.*

336. *See supra* notes 257–64 and accompanying text.

337. *See supra* note 218–22 and accompanying text.

inherent in the "predictable solutions" requirement of *KSR*'s obvious-to-try test.[338]

CONCLUSION

Innovation in the course of pharmaceutical research requires methodical, trial-and-error experimentation into largely unpredictable areas that the prior art identifies as most favorable for exploration.[339] Because of this, the obvious-to-try test—which discounts whether a researcher would have possessed any reasonable expectation that a successful result would be attained—disproportionately penalizes the patentability of pharmaceutical research results.[340] Accordingly, courts should acknowledge the context-specific nature of patent law[341] when applying the Supreme Court's recent obviousness pronouncement.[342] In particular, when contemplating the pertinence of the obvious-to-try test ostensibly adopted in *KSR International Co. v. Teleflex Inc.*,[343] courts should diligently enforce its meaningful "predictable solutions" circumscription.

The Federal Circuit's decision in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty.* wisely espoused this view, whereas the court imprudently adopted a misplaced obvious-to-try rationale in *Pfizer, Inc. v. Apotex, Inc*. On account of the disproportionate impact of the obvious-to-try test in the pharmaceutical arts, *Pfizer* should be limited to its "particularized facts,"[344] permitting the *Takeda* rationale to predominate in cases involving pharmaceutical inventions. In essence, this Note argues that, because predictability varies by discipline,[345] so too should the relevance of *KSR*'s obvious-to-try test. Courts must take care not to deny the patentability of pharmaceutical research results merely "because the researcher dared to follow a logical plan."[346]

338. *See* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350, 1359 (Fed. Cir. 2007) ("[T]his case fails to present the type of situation contemplated by the [Supreme] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.' The evidence showed that it was not obvious to try."); *see also supra* notes 220–22 and accompanying text.

339. *See supra* notes 294–95 and accompanying text.

340. *See id.*

341. *See* sources cited *supra* notes 47–50.

342. *See generally* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

343. *See id.* at 1742.

344. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367 (Fed. Cir. 2007) (emphasis omitted).

345. *See supra* notes 310–16 and accompanying text.

346. *See In re* Merck & Co., 800 F.2d 1091, 1100 (Fed. Cir. 1986) (Baldwin, J., dissenting).