

What is “Obvious To Try”?

The History, Meaning and Application of the Obvious-To-Try Test
as a Means for Proving Obviousness of Patent Claims

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For an invention to be patentable, its subject matter cannot be obvious. 35 U.S.C.A. § 103 (2004). The present paper first provides a brief overview of the law of obviousness. Then, it considers the history, meaning and application of the “obvious-to-try” test, whereby an invention may be deemed obvious if it was obvious to try. The Court of Appeals for the Federal Circuit (Federal Circuit) had criticized and unequivocally rejected this test in the past (See e.g., *In re Deuel*, 51F.3d 1552, 1559 (Fed. Cir. 1995)), but two years ago the Supreme Court suggested that the fact that an invention was obvious to try might suffice to prove obviousness in some circumstances. *KSR International v. Teleflex, Inc.* 550 U.S. 398, 127 S.Ct 1727, 1742 (2007). Since the *KSR* decision, the Federal Circuit’s application of the obvious-to-try approach has been controversial and raises important policy issues.

Introduction to the Law of Obviousness

Codification and Constitutional Significance of the Obviousness Requirement

The judiciary created the common law requirement that to be patentable, the construction of an invention consisting of a combination of old elements must require more “ingenuity and skill” than that “possessed by an ordinary mechanic acquainted with the business” *Hotchkiss v. Greenwood*, 52 U.S. 248, 267 (1851). Courts interpreted this requirement variably; therefore, patent lawyers sought a codification of the requirement that would clarify the standard of patentability. Craig A. Nard, *The Law of Patents* 326 (Aspen Publishers 2008). In response, Congress codified the requirement for non-obvious subject matter in § 103 of the 1952 Patent Act. Section 103(a) currently describes this requirement as follows:

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 negated by the manner in which the invention was made.

35 U.S.C.A. § 103(a) (2004). The Supreme Court held that the level of innovation necessary for patentability did not change with the enactment of section 103. *Graham v. John Deere*, 383 U.S. 1, 4 (1966). The Court noted that the non-obviousness requirement is not merely a judicial or statutory requirement but originates in the U.S. Constitution, which permits the grant of patents only for inventions that ‘promote the Progress of . . . useful Arts.’ *Id.* Granting patents for subject matter that is obvious would be contrary to this constitutional limitation and would effectively remove knowledge from the public. *Id.*

General Framework for the Analysis of Obviousness

In *Graham*, the Supreme Court characterized obviousness as a legal question that depends on three factual inquiries: (1) the scope and content of the prior art, (2) differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. *Id.* at 17. In addition, “[s]uch secondary considerations as commercial success, long-felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.” *Id.* at 17-18.

Application of the Law of Obviousness by the United States Supreme Court

Concurrent with *Graham*, the Supreme Court decided *United States v. Adams*, 383 U.S. 39 (1966). In concluding that Adams’ invention was not obvious, the Court emphasized that the results obtained with the claimed battery were “unexpected” and “far surpassed then-existing wet batteries.” *Id.* at 51. The prior art had predicted that the combination used in Adams’ invention would not be successful (i.e., the prior art taught away from the invention). *Id.* at 52. Experts had expressed disbelief in the operability of the invention, yet later some of these experts patented improvements on the same system. *Id.* The analysis in *Adams* indicates that factors

that should favor a finding of non-obviousness include unexpectedly good results that surpass results achieved in the prior art, results that are contrary to the predictions of the prior art (i.e., success despite “teaching away”) as well as results that are contrary to the predictions of experts in the field.

In contrast, the Supreme Court held obvious the claimed invention in *Anderson’s-Black Rock, Inc. v. Pavement Salvage Co., Inc.*, 396 U.S. 57 (1969). The claimed invention combined a radiant heat burner with a standard paving machine. Both the radiant heat burner and the paving machine were known in the prior art, but they had not previously used in combination.

Id. The Court suggested that when an inventor combines elements known in the prior art, synergism between elements is needed to support a finding of non-obviousness:

A combination of elements may result in an effect greater than the sum of the several effects taken separately. No such synergistic result is argued here. It is, however, fervently argued that the combination filled a long felt want and has enjoyed commercial success. But those matters ‘without invention will not make patentability.’

Anderson’s-Black Rock, 396 U.S. at 61 (citations omitted). The Court concluded that “while the combination of old elements performed a useful function FN4, it added nothing to the nature and quality of the radiant-heat burner already patented.” *Id.* at 62. Footnote 4 related obviousness to novelty. It quoted the language of 35 U.S.C. § 101 and added, “Absent here is the element ‘new.’ For as we have said, the combination patent added nothing to the inherent characteristics or function of the radiant-heat burner.” *Id.* at 63. Thus, the concept of inherency applies to obviousness. Just as discovering an inherent property of a claimed invention does not make the claimed invention novel (see e.g., *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1242 (Fed. Cir. 1999)), discovering an inherent property of an element of a claimed combination invention will not make the claimed combination non-obvious.

In its most recent obviousness determination, the Supreme Court held obvious a claimed invention that combined an electronic sensor with an adjustable automobile pedal. *KSR International v. Teleflex, Inc.* 550 U.S. 398, 127 S.Ct 1727 (2007). These elements were known individually in the prior art but had not previously been combined. The Supreme Court held the invention obvious, reversing the Federal Circuit. The Supreme Court cited three of its precedents (*United States v. Adams*, 383 U.S. 39 (1966); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co., Inc.*, 396 U.S. 57 (1969); *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976)) to support its conclusion that “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 127 S.Ct at 1739.

The Federal Circuit had held the invention in *KSR* to be non-obvious on the ground that the prior art did not contain a teaching, suggestion, or motivation (TSM) to combine the elements of the invention. Although the Supreme Court characterized the TSM test, which had been developed and used for many years by the Federal Circuit, as a “helpful insight,” the Court cautioned that the Federal Circuit’s overly strict application of the TSM test was incompatible with Supreme Court precedents:

The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. . . . In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

KSR, 127 S.Ct at 1741. Thus, the Supreme Court warns that the obviousness analysis should not rely on overly simplistic bright-line rules, such as requiring an explicit TSM in the prior art.

Rather, the Supreme Court advocates an “expansive and flexible” analysis. *Id.* at 1739. This analysis should be fact-specific, should rely on common sense, and should consider the reason behind the obviousness requirement, which is that the constitution permits patents for innovations that promote progress and not for minor advances that would occur “in the ordinary course.” *Id.*

In *KSR*, the Supreme Court stated that the Federal Circuit had erred in concluding “that a patent claim cannot be proved obvious merely by showing that the combination of elements was ‘obvious to try.’” *Id.* at 1742. The Court indicated that in some circumstances, the fact that a claimed invention was ‘obvious to try’ may be sufficient to prove obviousness:

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.”

KSR, 127 S.Ct at 1742 (emphasis added). This statement acknowledged that something that is obvious to try is not necessarily obvious, but the description of when such an invention is obvious leaves much interpretive leeway. All of the italicized words in the quotation above could be interpreted variably. For example, how many possible solutions can there be to consider the number “finite”? It is unlikely that the Court meant anything short of an infinite number of solutions. Under what circumstances should one consider a possible solution to have been previously “identified” and “predictable”? How likely must success be to consider it “anticipated”? To some extent, these themes have been treated previously in Federal Circuit jurisprudence, but it is unclear how closely the Federal Circuit will follow its own precedents after the Supreme Court’s critique of its approach to obviousness in *KSR*.

History of the Obvious-To-Try Test

The earliest Court of Customs and Patent Appeals (C.C.P.A.) case that used the phrase “obvious to try”¹ was the case of *In re Carpenter*, 151 F.2d 207 (C.C.P.A. 1945). Continuing until about 1963 the C.C.P.A. used or affirmed the language “obvious to try” in invalidating patent claims. See e.g., *In re Carpenter*, 151 F.2d 207 (C.C.P.A. 1945); *In re Leum*, 158 F.2d 311 (C.C.P.A. 1946); *In re Ruschetta*, 968 F.2d 687 (C.C.P.A. 1958); *In re Sejournet*, 285 F. 2d 823 at 825 (C.C.P.A. 1961); *In re Georgeff*, 291 F. 2d 941 at 944 (C.C.P.A. 1961); *In re Novak*, 306 F.2d 917 at 921 (C.C.P.A. 1962).

Starting in 1963, the court began criticizing the “obvious to try” analysis as contrary to the express language of the statute. *In re Huellmantel*, 324 F.2d 998 (C.C.P.A. 1963). The court in *Huellmantel* affirmed the PTO Board’s rejection of claims to a therapeutic chemical composition; however, the court criticized the Board’s analysis in footnote 3. *Id.* at 1003. The Board had found that the fact that the claimed chemical composition yielded improved results was not material to patentability because it was obvious to try to substitute one steroid for another. *Id.* The C.C.P.A. criticized this reasoning, noting that it conflicted with section 103:

We believe this reasoning, insofar as it negates consideration of properties in determining obviousness under section 103, flies in the face of the plain language of the statute as interpreted by this court. . . . Section 103 says, inter alia, ‘the subject matter as a whole would have been obvious* * *.’ Nothing 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.

Huellmantel, 324 F.2d at 1003. Thus, the “as a whole” language in what is now section 103(a) conflicts with at least some types of rejections based on obvious-to-try reasoning.

In addition, Federal Circuit judges have pointed out that the obvious-to-try analysis conflicts with the sentence of section 103 which states that “patentability shall not be negated

¹ based on a Westlaw Terms and Connectors search of “obvious-to-try” in the ctaf database.

by the manner in which the invention was made.” See *e.g.*, *In re Merck*, 800 F.2d 1091, 1099-1100 (Fed. Cir. 1986, Baldwin, J., dissenting). Even after *KSR* was decided, three Federal Circuit judges echoed this concern in their dissents from the denial for rehearing en banc in *Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1377, 1379, 1383,1384 (Fed. Cir. 2007) (Newman, Lourie & Rader, JJ., dissenting). (*Pfizer*, a panel decision that issued before *KSR*, held that the invention under consideration was obvious because it was made by “routine experimentation” that served only to verify predicted results. *Pfizer v. Apotex*, 480 F.3d 1348 at 1367 (Fed. Cir. 2007). The dissenting judges criticized this reasoning, in part because the last sentence of § 103(a) indicates that the fact that an invention was made by routine experimentation cannot properly support a finding of obviousness. 488F.3d at1377 at 1379, 1383, 1384.)

The Federal Circuit provided a more refined critique of the obvious-to-try analysis in the case of *In re O’Farrell*. 853 F.2d 894 (Fed. Cir. 1988). *O’Farrell* characterized two general types of situations where an “obvious to try” test leads to an erroneous false positive type of conclusion, that is, where something that is obvious to try is nevertheless non-obvious. In the first type of situation, numerous possible choices would be obvious to try (e.g., one could vary all possible parameters) but the prior art gives no guidance as to which of the choices is most likely to be successful. *Id.* at 903. In the second type of situation, it would be obvious to explore a new technology or general approach that seems promising, but the prior art gives only general guidance about the direction to be pursued. *Id.* *O’Farrell* also provides some guidance as to when an invention that is obvious to try is obvious, suggesting that predictability is what matters in the obviousness analysis:

Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of *unexpected results*, that would then provide an objective basis for

showing that the invention, although apparently obvious, was in law nonobvious. . . . For obviousness under §103, all that is required is a *reasonable expectation of success*.

O'Farrell, 853 F.2d at 903-904 (emphasis added; internal citations omitted).

Accordingly, showing that an invention had a “reasonable expectation of success” is sufficient to prove obviousness under *O'Farrell*. However, results that are unexpectedly good may effectively rebut a showing of obviousness based on the “reasonable expectation of success” standard. *Id.* *O'Farrell* is not merely of historical significance; the Federal Circuit recently re-affirmed the *O'Farrell* approach to obviousness, noting that this approach is consistent with *KSR*. *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).

Before *KSR*, *In re Deuel* was frequently cited for its admonition, “‘Obvious 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.’” 51F.3d 1552, 1559 (Fed. Cir. 1995). The Federal Circuit in *Deuel* held that DNA and cDNA molecules encoding a protein were not obvious over the combination of a prior art reference disclosing a partial amino acid sequence of a protein and a prior art reference teaching a general method of gene cloning. *Id.* at 1557. The court reasoned that a prima facie case of obviousness of a chemical structure requires that the prior art suggest the claimed compound, normally based on structural similarity of prior art compounds. *Id.* at 1558. However, a prior art protein is not structurally similar to the DNA that encodes it. *Id.* Disclosure of the amino acid sequence of a protein “does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of

DNA sequences coding for the protein.” *Id.* at 1558. *In re Kubin*, discussed below, has at least partially abrogated *Deuel*. 561 F.3d 1351 (Fed. Cir. 2009).

Public Policy Considerations

In addition to the concerns that the obvious-to-try test is contrary to section 103 and may lead to erroneous conclusions if applied as a bright-line rule, the obvious-to-try analysis raises policy concerns. In *In re Tomlinson*, the PTO examiner rejected the applicants’ claims, stating that ‘it would be obvious for a skilled chemist to try to stabilize polypropylene with a known stabilizer for polyethylene’, and it would be ‘routine experimentation for a skilled chemist to attempt to stabilize polypropylene against the deteriorative effect of light by first trying the known stabilizers for polyethylene.’ 363 F.2d 928, 931 (C.C.P.A. 1966). The PTO Board affirmed the rejection. The C.C.P.A. reversed the rejection in part and criticized the PTO’s use of an “obvious to try” analysis, because it was contrary to statute and contrary to public policy:

Our reply to this view is simply that it begs the question, which is obviousness under section 103 of compositions and methods, not of the direction to be taken in making efforts or attempts. Slight reflection suggests, we think, that there 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.’

Tomlinson, 363 F.2d at 931.

The incentive issue raised in *Tomlinson* remains pertinent. According to the “reasonable expectation of success” standard suggested in *O’Farrell*, 853 F.2d at 903-904 and re-affirmed in *Kubin* 561 F.3d 1351 (Fed. Cir. 2009), any invention that is made by pursuing research that has a reasonable expectation of success and that yields only the

expected success, as opposed to unexpectedly good results, is not patentable. Many shareholders of companies that invest heavily in research and development would be disappointed to learn that the only inventions that can be protected under our patent system are those that come from research that either (1) has no reasonable expectation of success or (2) serendipitously yields better than expected results.

Imagine the following scenario: making a new and important pharmaceutical X has a reasonable expectation of success but requires many years of effort and great expense. Under our patent system, the company that makes X cannot obtain a patent for X, because X is obvious. This result seems contrary to the public interest and contrary to the Supreme Court's reasoning regarding the policies that underlie the obviousness requirement. In *Graham*, the Court noted that the obviousness requirement derives from the constitutional mandate that patent system 'promote the Progress of . . . useful Arts.' *Graham*, 383 U.S. 1, 4. In *KSR*, the Court reasoned that the obviousness requirement should prevent the patenting of inventions that would be made "in the ordinary course," because allowing the patenting of such inventions would, in effect, remove knowledge from the public domain. 127 S.Ct at 1741. However, if there is no patent incentive that allows companies to profit from inventing pharmaceuticals like X, such pharmaceuticals may not be made in the ordinary course². (Cf. *In re Merck*, 800 F.2d 1091, 1100 (Fed. Cir. 1986) (Baldwin, J., dissenting). Judge Baldwin noted, "The obvious-to-try analysis is an attack on the method of making an invention that specifically penalizes people in areas of endeavor where advances are won only by great effort and expense. The

² Alternative types of incentives are possible. For example, the Waxman-Hatch Act provides a five-year period of market exclusivity as an incentive for the development of some types of new drug products even if the products are not patentable, and Congress is considering similar legislation for biologic drug products. Alfred B. Engelberg, Aaron S. Kesselheim, & Jerry Avorn, *Balancing Innovation, Access, and Profits – Market Exclusivity for Biologics*, 361 *New England Journal of Medicine* 1917 (2009).

pharmaceutical field is particularly hard hit because there is an overabundance of structures that are obvious to try.”)

A Better Standard For Assessing Obviousness?

Based on these public policy considerations, it appears that the obvious-to-try and “reasonable expectation of success” (RES) tests are not the optimal means for promoting the policy goals that the obviousness requirement was intended to promote. Because research must proceed in a manner that is reasonable, a higher standard of predictability than a “reasonable expectation” is needed to show that an invention is obvious, and it will be argued here that a higher standard is what the Supreme Court intended.

Like the Federal Circuit in *O’Farrell*, the Supreme Court in *KSR* focused on predictability; however, the Supreme Court’s description of an “identified, predictable solution” that yields “anticipated success” suggests a much higher degree of predictability than does *O’Farrell*’s “reasonable expectation of success.” Compare *KSR*, 127 S.Ct at 1742 with *O’Farrell*, 853 F.2d at 903-904. An “identified” solution means one that is recognized with particularity *Websters College Dictionary* (Random House, Inc. 1991). Thus, an “identified” solution is one that is selected from a larger group of possible solutions. A “predictable” solution is one that can be foretold “with precision of calculation, knowledge, or shrewd inference from facts or experience.” *Id.* An “anticipated” solution is one that can be realized or foreseen in advance. *Id.* In contrast, an “expectation” is merely an act of anticipating, or a “prospect of future benefit or fortune.” *Id.* Thus, the Supreme Court’s description of the “obvious to try” analysis in *KSR* suggests that proving obviousness requires a higher standard of proof than does a “reasonable expectation of success” standard.

There is also Federal Circuit precedent indicating that establishing obviousness should require a higher standard of proof. *In re Pantzer*, 341 F.2d 121 (C.C.P.A. 1965). *O'Farrell* cites two references for the “reasonable expectation of success” standard: *In re Longi*, 759 F.2d 887 (Fed. Cir. 1985) and *In re Clinton*, 527 F.2d 1226 (C.C.P.A. 1976). *O'Farrell*, 853 F.2d 894 at 904. *Clinton*, in turn, cites several other cases, the earliest of which is *In re Pantzer*, 341 F.2d 121 (C.C.P.A. 1965). *Clinton*, 527 F.2d at 1228. *Pantzer*, however, does not use the language “reasonable expectation of success;” instead, *Pantzer* describes the obviousness inquiry as follows:

The appellants' position appears to be that one must be able to predict with certainty that those glycols will dissolve methetharimide before the rejection is proper here.

However, as we pointed out in *In re Moreton*, 288 F.2d 940, 48 CCPA 928, obviousness does not require absolute predictability. Where, as here, the knowledge of the prior art clearly suggests that the use of glycols as solvents in place of water to form solutions of methetharimide stable against hydrolysis would be successful, the mere possibility of failure does not render their successful 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 [sic].

Pantzer, 341 F.2d 121, 126. The preceding sentence appears to be two sentences that are not properly separated. Thus, *Pantzer* seems to say that where there is a clear suggestion in the prior art that an invention will be successful, a mere possibility of failure does not make the invention non-obvious. *Id.* Moreover, the *Pantzer* court held that an invention would be obvious if one of ordinary skill in the pertinent art would consider it “logical to anticipate with a high degree of probability that a trial of [the claimed invention] would be successful.” *Id.*

Compared with the “reasonable expectation” standard, the *Pantzer* standard conforms more closely with the Supreme Court’s language indicating that an invention is

likely to be obvious if it was obvious for a person of ordinary skill in the art to try making it because it was one of a “finite number” of “identified, predictable solutions” that led to “anticipated success.” *KSR*, 127 S.Ct at 1742. The *Pantzer* standard would allow patenting of inventions where there was a reasonable expectation of success but where it was not logical to anticipate that there was a “high degree of probability” that the invention would be successful. The *Pantzer* standard makes better policy sense than does the current “reasonable expectation” standard, which suggests that only unreasonable or serendipitous research deserves a patent. Research must proceed in a reasonable manner. The patent incentive should reward inventors who pursue reasonable, yet risky research (i.e., it is not logical for a person of ordinary skill in the art to anticipate that the research will have a high probability of success) that yields a successful but not unexpected result.

The Federal Circuit’s Application of the Obvious-To-Try Test After *KSR*

Since the Supreme Court’s *KSR* decision, the Federal Circuit has applied the obvious-to-try test in relatively few cases, and the obvious-to-try analysis will likely continue to evolve. This paper will focus on the recent cases of *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), reh’g denied, 488 F.3d 1377 (Fed. Cir. 2007) (only the petition for panel rehearing and rehearing en banc was decided after issuance of the *KSR* decision), *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), and *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). The first three cases pertain to pharmaceutical inventions and the fourth case involves the patenting of a gene.

Pfizer v. Apotex

In *Pfizer v. Apotex*, the Federal Circuit reversed the district court's finding of validity and held obvious Pfizer's '303 patent, which claimed the besylate salt of the drug amlodipine, which is used to treat hypertension and angina. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), reh'g denied, 488 F.3d 1377 (Fed. Cir. 2007). Drugs such as amlodipine are made into acid addition salts to improve their bioavailability. Amlodipine besylate is made by reacting amlodipine with benzene sulphonic acid. *Id.* at 1353. The prior art considered for the obviousness analysis included the '909 patent of Pfizer and the Berge reference. The '909 patent had claimed pharmaceutically-acceptable acid addition salts of amlodipine and noted that the preferred salt was maleate. *Id.* at 1353. A list of possible acids was disclosed but neither benzene sulphonic acid nor the larger class of sulphonic acids was on the list. *Id.* at 1361. The Berge reference disclosed a list of 53 FDA-approved anions that had been used previously in making pharmaceutical salts. *Id.* at 1355. It disclosed that benzene sulphonate had a relative frequency of use of 0.25%. *Id.*

After submission of the prior art '909 patent, researchers at Pfizer had difficulties developing amlodipine maleate as a commercial drug product, because it was chemically unstable (it broke down when exposed to water) and too sticky (stuck to the manufacturing equipment, such as the press used for making tablets). *Id.* at passim. Researchers at Pfizer came up with a list of seven alternative anions that could be used to form acid addition salts with amlodipine and these were tested. *Id.* at 1354. According to the findings of the district court, amlodipine besylate was the most stable of the eight salts tested, and the maleate salt form was sixth on the list. *Id.* at 1357. Unlike

amlodipine maleate, amlodipine besylate did not undergo a Michael addition reaction when exposed to water. *Id.* Amlodipine besylate was also less sticky and easier to process into tablets than the maleate form. *Id.*

The district court found that there was no reasonable expectation of success in making amlodipine besylate, because the prior art as well as expert testimony on both sides taught that there is no way of predicting the influence of a particular salt species on the behavior of a parent compound. *Id.* at 1357. The besylate salt form was unexpectedly superior in terms of its properties, such as solubility, stability, and processability. *Id.* The district court found that the besylate salt was not obvious in light of the Berge reference, because Berge disclosed that benzene sulphonate was used at a frequency of only 0.25% or 1/400 and because the examiner must have considered Berge, which was cited in the '303 patent. *Id.* at 1356.

The Federal Circuit concluded that the district court clearly erred in concluding that there was no reasonable expectation of success in making amlodipine besylate. *Id.* at 1365. First, the court reasoned that Berge showed that the genus of FDA-approved anions was small, and the fact that benzene sulphonate was used at a low frequency was not highly probative, because almost all of the anions, except hydrochloride, were used at low frequencies. *Id.* at 1363. Second, the district court ignored the significance of other prior art references that could have allowed a person of ordinary skill in the art to narrow the genus of pharmaceutically acceptable anions. *Id.* These references showed that the besylate salt form was useful in promoting stability and solubility of pharmaceuticals. Third, the testimony of a Pfizer researcher and Pfizer's supplemental FDA filing showed

that there was an expectation that amlodipine besylate would work for its intended purpose. *Id.* at 1364.

The Federal Circuit found that amlodipine besylate was obvious to try and obvious to make. *Id.* at 1366. The court stated, “[W]e hold that optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious where as here the acid addition salt formulation has no effect on the *therapeutic effectiveness* of the active ingredient and the prior art heavily suggests the particular anion used to form the salt.” (Emphasis added.) *Id.* at 1368. The court found this case analogous to other cases that held that the optimization of a range or other variable within the claims was obvious. *Id.* Further, the court reasoned that this case did not fall into one of the *O’Farrell* exceptions, because the only parameter to be varied was the anion with which to make the salt, and the prior art provided specific guidance that would have allowed a person of ordinary skill to narrow the list of possible anions to only a few. *Id.* at 1366.

The dissents from the denial for rehearing criticized the reasoning of the panel that decided *Pfizer*. 488 F.3d 1377. First, the panel emphasized that the besylate salt did not influence the therapeutic effect of the claimed invention, apparently neglecting its other unexpectedly good properties such as stability and nonstickiness. *Id.* at 1381, 1384 (Lourie, Rader, JJ., dissenting). Second, the argument regarding routine experimentation or routine optimization is contrary to the last sentence of section 103(a). *Id.* at 1379, 1383, 1384 (Newman, Lourie, Rader, JJ., dissenting). Third, the panel should have deferred to the district court’s factual findings that there was no reasonable expectation of success and that it produced unexpected results. *Id.* at passim (Newman, Lourie, Rader,

JJ., dissenting). Fourth, the reasonable expectation of success alleged by the panel improperly rested on the experimenter's subjective expectations. *Id.* at 1383, 1384 (Lourie, Rader, JJ., dissenting). Finally, obvious-to-try jurisprudence does not work well with unpredictable pharmaceutical inventions. *Id.* at 1384 (Rader, J., dissenting).

Pfizer might have come out differently if Pfizer had emphasized that many variables, in addition to the type of salt, play a role in developing a commercial drug product. For example, the inactive ingredients in the tablet and the type of coating applied to it would also influence stability and stickiness. These variables would interact in an unpredictable manner with the type of salt chosen. Because there were many parameters that could have been varied, it could have been argued that this case should fall under the first *O'Farrell* exception.

Sanofi-Synthelabo v. Apotex

The Federal Circuit held non-obvious the Sanofi '265 patent's claim to the hydrogen sulfate salt of the dextro-rotatory isomer of the pharmaceutical compound PCR4099 (common name clopidogrel), which is used to prevent blood clots. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008). Prior art patents had claimed PCR4099 and had mentioned generally that its enantiomers could be separated if desired. *Id.* at passim. However, the '265 patent disclosed that the substantially separated dextro-rotatory isomer had advantages over the racemic mixture (i.e., the mixture of dextro-rotatory and levo-rotatory isomers) that Sanofi had previously been using and had disclosed in the prior art patents, because the dextro-rotatory isomer provided all of the therapeutic activity of the racemate and had no significant neurotoxicity, whereas the

levo-rotatory isomer produced neurotoxic effects and was not therapeutically effective (this is called absolute stereospecificity). *Id.* at 1081.

The Federal Circuit affirmed the district court in holding non-obvious the claim to the hydrogen sulfate salt of the substantially separated dextro-rotatory isomer of PCR4099. *Id.* at 1090. The court reasoned that there was no reasonable expectation of success in this case, because procedures for separating enantiomers were unpredictable, difficult and not routine. *Id.* at 1088. The absolute stereospecificity of the separated isomers was an unexpectedly good result, because absolute stereospecificity is rare. The court distinguished *Pfizer*, because here there was no evidence that a person of ordinary skill in the art could have narrowed the possible salts to only a few, and the prior art taught away from the use of sulfuric acid with an enantiomer. *Id.* at 1088-1089.

As a secondary consideration favoring non-obviousness, the court noted that Sanofi had expended tens of millions of dollars and several years in developing the racemate before separating the enantiomers. *Id.* at 1088. The latter consideration contrasts with *Pfizer*, where the court said that such an objective consideration “seemed suspect” when there was no evidence in the record to support the “implicit finding” that Pfizer had abandoned amlodipine or stood to lose significant time and investment dollars. *Pfizer*, 408 F.3d at 1369. The *Sanofi* position makes more sense. A company would not unnecessarily expend significant time and financial resources on an invention before pursuing a better alternative variant of that invention if the better variant were obvious.

Takeda v. Alphapharm

The Federal Circuit held non-obvious a claim to an antidiabetic compound called pioglitazone that was structurally similar to a prior art compound in *Takeda Chemical*

Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007). Alphapharm asserted that pioglitazone was obvious in light of the prior art “compound b.” *Id.* at 1354. Pioglitazone and compound b are identical except for the substituents attached to a pyridine ring moiety. *Id.* at 1353-1354. Compound b has a methyl group on the 6-position and no substituents on the 5-position of the pyridine ring, whereas pioglitazone has an ethyl group on the 5-position and no substituents on the 6-position. *Id.*

The Federal Circuit affirmed the district court’s finding that the claim to pioglitazone was non-obvious. *Id.* at 1352. First, the court held that when a claimed compound is structurally similar to a prior art compound, to establish that the claimed compound is prima facie obvious, the challenger of the patent must show that there is a “reason that would have led a chemist to modify the prior art compound in a particular manner.” *Id.* at 1357. The Federal Circuit found this rule consistent with *KSR*, because *KSR* had rejected only the rigid application of the TSM test and had “acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.” *Id.* at 1356-1357 (citation omitted).

Second, the Federal Circuit held that Alphapharm had failed to make a prima facie showing of obviousness and rejected Alphapharm’s claim that it would have been obvious to try to modify compound b to make pioglitazone. The prior art had disclosed many possibilities of starting compounds (“lead compounds”) and many possible modifications that could have been made to these compounds. *Id.* at 1357-1362. The prior art also taught away from compound b as a lead compound. *Id.* at 1358-1359. There was nothing in the prior art to provide a reasonable expectation that modifying

compound b by homologation (here, adding a methyl group) and ring-walking would produce the observed reduction in toxicity, which was an unexpectedly good result. *Id.* at 1360-1362.

In re Kubin

The Federal Circuit held obvious a claim to a genus of DNA that included the species encoding a known protein in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). Appellants claimed “an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.” *Id.* at 1353. SEQ ID NO:2 was the sequence that appellants disclosed for the CD48-binding region of the protein Natural Killer Cell Activation Inducing Ligand (NAIL). *Id.* The USPTO Board rejected the claim for lack of written description³ and because it was obvious over two prior art references⁴, Sambrook and Valiante. *Id.* 1353-1354. Sambrook was a lab manual on cloning methods. *Id.* at 1354. Valiante disclosed p38 receptor protein, which is the same as NAIL, but did not disclose its amino acid sequence. *Id.* Valiante claimed a monoclonal antibody specific for p38 and described a cloning protocol for isolating and identifying p38, noting that its DNA and protein sequences could be obtained by conventional methods. *Id.*

³ The Federal Circuit did not reach the written description issue and it will not be discussed here.

⁴ The Board also considered the Matthew reference, describing it as cumulative with Sambrook and Valiante. *Kubin*, 561 F.3d at 1354. Matthew disclosed 2B4, a monoclonal antibody for 2B4, and a method for cloning its gene. *Id.* at 1355. Matthew’s data identified a human homolog of the 2B4 gene but suggested that the 2B4 gene is not expressed in humans. *Id.* at 1357. The Board determined that 2B4 was the murine equivalent of NAIL. *Id.* at 1355. The Federal Circuit found that “substantial evidence supports the Board’s conclusion that Matthew reinforces the relative ease of deriving the claimed sequence following the teachings of the prior art.” *Id.* at 1357. However, Matthew should not have been considered as prior art, because only after Kubin’s filing date was the 2B4 gene found to be the mouse homolog for human NAIL. Kevin E. Noonan, Patentdocs.org, *In re Kubin* (Fed. Cir. 2009), <http://www.patentdocs.org/2009/04/in-re-kubin-fed-cir-2009.html> (April 15, 2009).

The Board found that NAIL's importance in the human immune response would have motivated one of ordinary skill in the art to isolate NAIL cDNA using conventional methodologies. *Id.* at 1355. The Board found that the appellants had used conventional techniques such as those in Sambrook to isolate and sequence the gene that codes for NAIL. *Id.* The Board also found that appellants had used the commercial monoclonal antibody disclosed by Valiante to isolate their claimed DNA sequence from a cDNA library. *Id.*

The Federal Circuit affirmed the Board's finding that there was a reasonable expectation of success in obtaining the claimed invention, because the prior art taught "a protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody specific to the protein for cloning this gene." *Id.* at 1360. The Federal Circuit stated that the Supreme Court in *KSR* had discredited *Deuel*, "*insofar as* [it] implies the obviousness inquiry cannot consider that the combination of the claim's constituent elements was 'obvious to try.'" *Id.* at 1358 (emphasis added). The court reasoned that the *Kubin* facts did not fit into either of the two *O'Farrell* exceptions and affirmed the Board's conclusion that *Kubin*'s claim was obvious. *Id.* at 1367. The court re-affirmed the conclusion of *O'Farrell* that an obviousness finding is appropriate "where the prior art '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.'" *Id.* at 1360 (citing *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988)). The fact that *Kubin*'s claim mentioned CD48 binding did not make the claim non-obvious, because this was an inherent feature of cDNA encoding NAIL. *Id.* at 1357. The Federal Circuit

declined to limit *KSR*'s application to predictable mechanical arts, as opposed to "unpredictable" fields such as biotechnology. *Id.* at 1360.

Critics of *Kubin* maintain that judges on the Federal Circuit failed to understand critical factual differences between the prior art and Kubin's invention. See e.g., Kevin E. Noonan, Patentdocs.org, *In re Kubin* (Fed. Cir. 2009), <http://www.patentdocs.org/2009/04/in-re-kubin-fed-cir-2009.html> (April 5, 2009). The *Kubin* court stated that "[T]he record shows repeatedly that Valiante's Example 12 [the proposed cloning protocol] produces for any person of ordinary skill in this art the claimed polynucleotide." *Id.* (citing *In re Kubin*, 561 F.3d 1351, 1356 (Fed. Cir. 2009)). However, at least some of the facts did not support this assertion. *Id.* Kubin's Appeal Brief to the Board argued that the prior art provided no guidance on how to treat human natural killer (NK) cells so that they would produce sufficient NAIL mRNA to be detectable in a cDNA library. *Id.* Kubin's patent explains that the library used was made from NK cells stimulated with a specific cocktail of activator molecules, and this treatment was not taught in the art. *Id.* Kubin's brief to the Federal Circuit argued that the evidence of record showed that the appellants did not use conventional methods to clone NAIL. *Id.*

Responding to and Preventing Obvious-To-Try Challenges

This section considers the practical implications of current obviousness jurisprudence: how can patent practitioners draft patent applications to prevent obvious-to-try challenges or respond to such challenges when they occur? Specific responses for gene patents and chemical patents will be considered, and then a general set of possible arguments that could be used with any type of patent will be outlined. Citations to

specific cases are not provided for every point in this section, because the relevant cases are discussed above.

Gene Patents

The *Kubin* court did not expressly overrule *Deuel* but only stated that *KSR* abrogated *Deuel* “insofar as” it rejected consideration of the fact that something was obvious to try in the obviousness inquiry. *Id.* When the claim to a gene is challenged because it was “obvious-to-try” to obtain the gene, it may be argued that *Kubin* is distinguishable on its facts, because the prior art in *Kubin* provided all of the following: a known protein, which could be expressed on a phage expression library; a monoclonal antibody specific to the protein; a proposed method of how to clone the gene and an example of a third party using the method to clone an ortholog. *Id.*

Chemical Patents

When a chemical compound is claimed that is similar to a prior art structure, it may be argued that there is no reason that would have led a chemist to modify the prior art compound to obtain the claimed structure. Cf. *Takeda* 492 F.3d 1350. Also, it can be argued that there were many possible prior art compounds that could have been modified and many ways they could have been modified.

Any Kind of Patent

General arguments against an obvious-to-try rejection include the following:

1. Even if the invention was obvious to try, it falls into one (or both) of the O’Farrell exceptions, because (a) there were many choices or parameter variations that could have been pursued and the prior art gave little guidance about which was likely to be successful, and/or (b) the prior art described only a generally promising field of endeavor

but did not provide specific guidance. In addition, the prior art did not contain detailed enabling methodology for practicing the claimed invention.

2. A person of ordinary skill in the relevant art would not have had a reasonable expectation of success, for reasons such as the following: (1) the prior art taught away from the claimed invention, (2) experts did not believe the claimed invention would work, (3) other experts had failed in making the claimed invention or in achieving what it achieved, (4) the inventor or owner of the patent unnecessarily expended a great deal of money, time, or other resources in pursuing an alternate invention that was not as good before discovering the claimed invention, (5) there were many parameters that could be varied and the outcome of varying them was unpredictable, (6) the type of experimental methods developed to make the claimed invention were not routine. An important caveat is that one must be careful in arguing that the experimentation used to make the invention was not routine or produced unpredictable outcomes, because this could induce an enablement rejection or future enablement challenge if the patent is litigated.

3. The results obtained were unexpected, far surpassing those of the prior art. This argument may be especially important when one is claiming a species that is part of a genus that was claimed in the prior art. One Federal Circuit judge argued that “[A] species should be patentable over a genus claimed in the prior art only if unexpected results [are] established,” although the law is currently “less than clear” on this point. *Takeda* 492 F.3d at 1364 (Dyk, J., concurring).

4. Presumably because of the way the Supreme Court’s description of the obvious-to-try approach begins (“When there is a design need or market pressure to solve a problem”), one commentator has suggested that it may be better if the patent specification does not

state that the problem solved by the invention was known. Kristina Caggiano, Pharmexec.com, Coping With Kubin, <http://license.icopyright.net/user/viewFreeUse.act?fuid=Mjc3MjQzMw%3D%3D> (Jan. 6, 2009). Instead, the specification should describe the problem that the invention addresses in novel terms, or discuss how some aspect of the problem was not known in the prior art. *Id.*

What Would Improve the Current Law of Obviousness?

A previous law review article that critically assessed obvious-to-try jurisprudence raised the concern that the obvious-to-try standard was being used to invalidate patents on inventions that had no reasonable expectation of success. Andrew V. Trask, “*Obvious to Try*”: *A Proper Patentability Standard in the Pharmaceutical Arts?* 26 Fordham L. Rev. 2625 (2008). The post-*KSR* cases discussed here have clearly enunciated that the relevant standard is still a “reasonable expectation of success.” This paper has argued that the “reasonable expectation of success” standard does not make sense in terms of policy, because it means that only research that has no reasonable expectation of success can be patented. Because research must proceed in a manner that is reasonable, it would be better if the Federal Circuit would return to the *Pantzer* “logical,” “high degree of probability” of success standard. This standard conforms more closely with the Supreme Court’s description of the obviousness inquiry in *KSR*. The *Pantzer* standard would make it less likely that patents would be invalidated as obvious, and under this standard, cases such as *Pfizer* and *Kubin* might be decided differently. The most important point is that the *Pantzer* standard would reward reasonable, yet risky research with a patent incentive.