PHARMA'S NONOBVIOUS PROBLEM

by
Rebecca S. Eisenberg[*]

This Article considers the effect of the recent decision of the U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. *on the nonobviousness standard for patentability as applied to pharmaceutical patents. By calling for an expansive and flexible analysis and disapproving of the use of rigid formulas in evaluating an invention for obviousness,* KSR *may appear to make it easier for generic competitors to challenge the validity of drug patents. But an examination of the Federal Circuit's nonobviousness jurisprudence in the context of such challenges reveals that the Federal Circuit has been employing all along the sort of flexible approach that the Supreme Court admonished it to use in* KSR. *The decisions of the Federal Circuit considering obviousness challenges to pharmaceutical patents suggest that the pharmaceutical industry does indeed have a nonobviousness problem, but that problem is not* KSR. *Rather, the problem is that many of the patents that the industry relies upon are invalid for obviousness under time-honored patent doctrine. Although perhaps able to survive the limited scrutiny that is possible on the basis of the information available at the prosecution stage, these patents cannot withstand a validity challenge with the benefit of a full evidentiary record at the infringement stage. It is more difficult to conduct an expansive and flexible analysis with limited information.* KSR *is more likely to have an impact on pharmaceutical patents if it makes it easier for the PTO to reject patent applications for obviousness in the first instance. It remains to be seen whether it will do so.*

[*] © 2007 Rebecca S. Eisenberg. Robert & Barbara Luciano Professor of Law, University of Michigan Law School. I am grateful to Rochelle Cooper Dreyfuss, Paul Johnson, Mark Lemley, Jessica Litman, Margaret Jane Radin, and workshop participants at the University of Michigan Law School, University of Arizona Law School, and Lewis & Clark Law School for helpful comments on earlier drafts of this paper.

I. INTRODUCTION

In *KSR International Co. v. Teleflex Inc.*,[1] the U.S. Supreme Court admonished the Court of Appeals for the Federal Circuit to avoid the use of "rigid and mandatory formulas" in applying the (non)obviousness standard for patentability.[2] At issue in that case was the Federal Circuit's application of the so-called "TSM" test, which calls for finding a "teaching, suggestion, or motivation" to combine elements from the prior art before holding a new combination of old elements to be obvious.[3] But the opinion suggests that the Supreme Court is more broadly skeptical of efforts to reduce the (non)obviousness inquiry to a formula, preferring the "expansive and flexible approach" that has characterized its own decisions on the issue over the past 150 years.

An important question that has surfaced in early commentary about the *KSR* decision[4] is its impact on pharmaceutical patents.[5] The

[1] 127 S. Ct. 1727, 1741 (2007).

[2] 35 U.S.C. § 103(a) (2000). In the text I use the term "(non)obviousness," with internal parentheses around the prefix, to mean "obviousness or nonobviousness."

[3] *KSR Int'l Co.*, 127 S. Ct. at 1730. Prior to the *KSR* decision, the Federal Circuit required finding a teaching suggestion or motivation to make the claimed invention in order to find it obvious when the invention combined elements from the prior art or otherwise modified the prior art. The required teaching, suggestion, or motivation could be found in the prior art itself, in the nature of the problem, or in the knowledge of a person having ordinary skill in the field. *See, e.g.*, *In re* Dembiczak, 175 F.3d 994 (Fed. Cir. 1999); *In re* Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

[4] *E.g.*, Posting of Jacob Goldstein to Wall Street Journal Health Blog, *Supremes' Decision Leaves Pharma Patents Vulnerable*, http://blogs.wsj.com/health/2007/04/30/supremes-decision-leaves-pharma-patents-vulnerable (Apr. 30, 2007, 18:11 EST); Harold C. Wegner, Post-*KSR* Chemical Obviousness in Light of *Pfizer v. Apotex* (June 13, 2007) (unpublished manuscript, http://www.patenthawk.com/blog_docs/070613_PostKSRChemicalObviousness.pdf); D. Benjamin Borson, KSR v. Teleflex, Inc.*: The Supreme Court Reviews Obviousness*, 89 J. PAT. & TRADEMARK OFF. SOC'Y 523 (2007); Steven J. Lee & Jeffrey M. Butler, *Teaching, Suggestion and Motivation:* KSR v. Teleflex *and the Chemical Arts*, 17 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 915 (2007).

[5] Although the invention at issue in *KSR* was not a chemical or pharmaceutical, amicus briefs alerted the court to the potential impact of the case on the pharmaceutical patents. The Pharmaceutical Research and Manufacturers of America (PhRMA) filed an amicus brief in support of respondents arguing that the Federal Circuit's TSM test provides a workable and objective standard of patentability that gives its members confidence that they can enforce their patents against free riders. *See* Brief of *Amicus Curiae* for Pharmaceutical Research and Manufacturers of America in Support of Respondents, KSR International v. Teleflex Inc., 127 S. Ct. 1727 (2007) (No. 04-1350), *available at* http://supreme.lp.findlaw.com/supreme_court/briefs/04-1350/04-1350.mer.ami.pharm.pdf. On the other side, the AARP filed an amicus brief arguing that the Federal Circuit's TSM test made it too easy to get patents on obvious combination drugs. *See* Brief of AARP, et. al. as *Amici Curiae* in Support of Petitioner, KSR International Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007) (No. 04-

pharmaceutical industry is famously dependent upon patent protection to exclude generic competitors from the markets for new drugs, but not all of the patents that support exclusivity cover breakthrough inventions. Many patents cover variations on successful drugs, such as metabolites, different salts, or stereoisomers of the active ingredient, new formulations such as time-release capsules or larger dosages that can be taken less frequently, or new combinations of old drugs. The *KSR* decision could potentially strengthen the hand of generic drug companies who challenge the validity of these patents by making it easier to show that the claimed inventions would have been obvious at the time they were made.

One reason to expect as much is that the Federal Circuit and its predecessor, the Court of Customs and Patent Appeals (CCPA), have articulated an approach to evaluating the (non)obviousness of chemical inventions, including pharmaceuticals, that sometimes seems as "rigid and mandatory" as the TSM approach at issue in *KSR*. Under this approach, a patent examiner (or a challenger of an issued patent) must first show that a claimed molecule is prima facie obvious by identifying a "structurally similar" molecule in the prior art and by showing motivation to modify that prior art molecule to create the claimed invention. The inventor may then overcome the prima facie case of obviousness by showing "surprising properties" for the claimed molecule not present in the prior art.[6] This approach originally forced patent examiners to be less rigid in evaluating the patentability of modified chemicals, by directing them to consider properties as well as structure.[7] In some biotechnology cases, however, it has functioned as a virtual per se rule of nonobviousness for molecules that are not structurally similar to molecules disclosed in the prior art.[8] To the extent that *KSR* disapproves the use of such "rigid and mandatory formulas," it calls into question the Federal Circuit's approach to chemical (non)obviousness.

Moreover, the most compelling argument in support of the TSM approach loses some of its force in the chemical context. That argument is that the discipline of identifying a teaching, suggestion or motivation

1350), *available at* http://supreme.lp.findlaw.com/supreme_court/briefs/04-1350/04-1350.mer.ami.aarp.pdf.

[6] *In re* Dillon, 919 F.2d 688, 692–93 (Fed. Cir. 1990).

[7] *In re* Papesch, 315 F.2d 381, 386 (C.C.P.A. 1963).

[8] For example, in *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), the Federal Circuit held that a DNA sequence encoding a polypeptide for which the prior art disclosed a partial amino acid sequence was nonobvious, although the prior art provided ample motivation to clone the DNA sequence with all but certain success. Since the partial amino acid sequence was not "structurally similar" to the claimed DNA sequence, the court concluded that the PTO had failed to establish that the DNA sequence was prima facie obvious. Following *KSR*, the PTO appears to be reconsidering the vitality of *In re Deuel*. *See Ex parte* Kubin, 83 U.S.P.Q.2d 1410 (Bd. Pat. App. & Interf. 2007); Examination Materials 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. 57526, 57532 (Oct. 10, 2007). See *infra* notes 150–53 and accompanying text.

to make the invention prior to the inventor's own contribution tends to counteract the "hindsight bias" that confounds efforts to evaluate, after the fact, whether an invention would have been obvious at the time it was made. The Federal Circuit has quite explicitly deployed the TSM approach to guard against the "hindsight trap" that makes a new invention seem obvious once an examiner or trial court knows what it is, even though the same invention might not have been obvious at the time it was made to an evaluator who only knew the prior art and was not yet aware of the inventor's further contribution.[9] By situating nonobviousness analysis more explicitly in the pre-invention state of the world, perhaps the TSM approach mitigates the hindsight bias.[10]

In the chemical context, the courts have had a different concern. Although the hindsight bias could work against the patentability of some chemical and pharmaceutical inventions, often these inventions appear less obvious in hindsight than they seemed ex ante. Many standard modifications of prior art molecules are obvious at least in the sense that a chemist of ordinary skill would be motivated to make them and would know how to make them, although there may be some uncertainty in predicting the properties of the resulting molecules. Small changes in the structure of a molecule sometimes bring about important changes in properties. Surprising properties may show that a molecule that appeared "structurally obvious" in light of the prior art is in fact a nonobvious invention. These properties can only be observed ex post, after the molecule has been made.

Although the rules for determining prima facie obviousness of new chemicals echo the TSM approach in the use of rigid rules to protect against hindsight, the rules for rebutting a prima facie case of obviousness do the opposite. Rather than guarding against the use of hindsight by situating the analysis in the pre-invention state of the world, once prima facie obviousness is established the Federal Circuit's chemical (non)obviousness analysis calls for the use of post-invention evidence to compare the properties of new chemicals with those of the prior art. It may even be necessary for an inventor to do further research after reducing a new chemical to practice in order to show that surprising properties of the new invention were not inherently present in

[9] *In re* Kahn, 441 F.3d 977, 987 (Fed. Cir. 2006); *In re* Kotzab, 217 F.3d 1365, 1369–71 (Fed. Cir. 2000); *In re* Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999). Recent empirical work supports the Federal Circuit's concern, suggesting that it is extremely challenging for people to ignore their knowledge of the invention and to make faithful ex ante evaluations of nonobviousness. Gregory N. Mandel, *Patently Non-Obvious: Empirical Demonstration that the Hindsight Bias Renders Patent Decisions Irrational*, 67 OHIO ST. L.J. 1391, 1393–94 (2006) [hereinafter Mandel I]; Gregory N. Mandel, *Patently Non-Obvious II: Experimental Study on the Hindsight Issue Before the Supreme Court in* KSR v. Teleflex, 9 YALE J.L. & TECH. 1, 3 (2006) [hereinafter Mandel II].

[10] Professor Mandel, although supporting retention of the TSM test, is equivocal about whether it succeeds as a safeguard against the hindsight bias. See Mandel I, *supra* note 9, at 1425–36.

structurally similar prior art chemicals. Rather than reminding examiners and trial courts to confine their analysis to what would have been apparent at the time the invention was made, the chemical (non)obviousness rules thus invite them to consider new evidence that was not available at the time of the invention. The chemical (non)obviousness approach may thus suffer from the rigidity of the TSM approach without the compensating virtue of situating the analysis in an ex ante time frame.[11]

Before such post-invention evidence becomes relevant to rebut a prima facie case of obviousness, it is first necessary to show that the invention is prima facie obvious, and this prima facie showing, like the TSM test, is firmly anchored in an ex ante time frame. In a subset of chemical patent cases involving claims to DNA sequences, the Federal Circuit has applied the prima facie obviousness prong of its chemical obviousness approach to establish, through a rigid rule, the nonobviousness of inventions that might seem obvious under a more expansive and flexible approach.[12] These cases seem inconsistent with *KSR* and, should the Federal Circuit persist in this approach, it may be vulnerable to another reversal by the Supreme Court.

The Federal Circuit articulates a similar proof structure in cases considering the (non)obviousness of pharmaceutical patents. But recent cases from the Federal Circuit considering the (non)obviousness of pharmaceutical inventions reveal little of the rigidity of the DNA patent cases, instead deploying the same tools with greater flexibility and nuance. Many of these cases review decisions of U.S. District Courts in patent infringement litigation at the point of generic entry into the market for already successful pharmaceutical products, rather than reviewing decisions of the PTO at the patent application stage. Far from deciding these cases according to a rigid formula, the Federal Circuit displays considerable sensitivity to context in evaluating each case on its facts, with considerable deference to trial court findings. For the most part, these cases do not support a view of the Federal Circuit as biased in favor of patentability. Instead, most panels use the Federal Circuit's doctrinal toolset, drawing on both its standard "TSM" approach and the special rules for determining chemical obviousness, to distinguish between inventions that required more than ordinary skill or achieved surprising results and inventions that merely combined or modified old products in predictable ways. The result is a growing body of case law

[11] To be sure, the use of hindsight in response to a prima facie showing of obviousness often supports patentability, *e.g.*, Knoll Pharm. Co. v. Teva Pharm. USA, 376 F.3d 1381, 1385 (Fed. Cir. 2004), while in other contexts the use of hindsight may be more likely to undermine patentability. But the selective use of hindsight only when it favors patentability at a minimum calls into question the meaning of the anti-hindsight shibboleth in (non)obviousness jurisprudence. Is the point to evaluate the invention at the time it was made, or is the point to support patentability by choosing the time frame that is most favorable to the inventor?

[12] See *infra* notes 126–49 and accompanying text.

invalidating for obviousness patents on modest changes to pharmaceutical products that were already in the prior art at the time of the invention. Some of these patents may succeed in forestalling generic entry for a while, but ultimately fail to withstand validity challenges in litigation.

In short, a review of the decisions of the Federal Circuit evaluating the (non)obviousness of pharmaceutical patents in infringement actions suggests that, in this particular context, the Federal Circuit for the most part has been doing all along what the *KSR* court is now telling it to do. If the pharmaceutical industry has a problem defending the nonobviousness of its inventions in litigation, that problem appears to predate *KSR*. Rather than fortifying the (non)obviousness standard for pharmaceutical inventions, perhaps *KSR* is more likely to lead the Federal Circuit to apply similar rigor in cases involving simple mechanical inventions.

But the pharmaceutical patent cases also show the limits of a nuanced, case-by-case approach. Case-by-case analysis is costly, uncertain, and time-consuming. A motivated challenger may find it worthwhile to attempt the necessary showing in order to compete in the lucrative market for a successful drug, but a patent examiner has fewer resources available to establish obviousness at the application stage. While litigants develop and courts evaluate a full evidentiary record in infringement litigation, the patent remains in force, and the public pays a premium for a product that should be available at competitive prices. For *KSR* to clear the pharmaceutical marketplace of invalid patents on obvious inventions, it would have to embolden examiners to reject the claims in the first instance, on the basis of a more limited record and analysis.

Part II reviews the Federal Circuit's TSM test as a mechanism for guarding against the hindsight bias and considers conflicting scholarly accounts of how that test functions on the ground. Part III analyzes the *KSR* decision and considers the extent to which it calls for departures from the Federal Circuit's approach and the extent to which it affirms that approach. Part IV reviews the distinct judicial approach to (non)obviousness for chemical patents, including biopharmaceutical patents, which has long sanctioned the use of post-invention evidence as to the differences between the invention and the prior art to show that inventions that may have appeared obvious at the time they were made are nonetheless patentable. Part V turns to a closer examination of the (non)obviousness jurisprudence of the Federal Circuit in the specific context of pharmaceutical patents. I conclude that in those cases, which primarily involve appeals from district court judgments in infringement actions, the Federal Circuit does not display the sort of rigid, formulaic, pro-validity analysis for which it has sometimes been faulted. Instead, in this particular context, the Federal Circuit appears to have been deploying all along an expansive and flexible approach. But although the Federal Circuit has been willing to affirm the invalidity of litigated drug patents on fully developed evidentiary records, it remains to be seen how

far it will be willing to affirm rejections on the basis of more preliminary showings at the prosecution stage.

II. TSM AND THE HINDSIGHT BIAS

The (non)obviousness standard for patent protection determines how much an invention must differ from the prior art in order to qualify for a patent. In theory, such a standard prevents the issuance of patents on inventions that, although new, are so close to the prior art that they are likely to be forthcoming even without the incentive of a patent.[13] Section 103(a) of the Patent Act articulates the basic standard 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.[14]

This is an explicitly hypothetical inquiry, an ex post evaluation to determine whether the invention *would have been obvious at the time it was made* to a hypothetical evaluator, *a person having ordinary skill in the art* (PHOSITA).

The Supreme Court, in its first encounter with this statutory language in *Graham v. John Deere*, elaborated on the proper approach to evaluating an invention for obviousness as follows:

> 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. Against this background, the obviousness or

[13] Graham v. John Deere Co., 383 U.S. 1, 11 (1966) ("The inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent."). *See also* Edmund W. Kitch, Graham v. John Deere Co.: *New Standards for Patents*, 1966 SUP. CT. REV. 293, 301 (1966) ("The non-obviousness test makes an effort, necessarily an awkward one, to sort out those innovations that would not be developed absent a patent system . . . . the focus has always been on the question whether the innovation could have been achieved by one of ordinary skill in the art, or whether its achievement is of a greater degree of difficulty."); Glynn S. Lunney, Jr., *E-Obviousness*, 7 MICH. TELECOMM. & TECH. L. REV. 363, 385–86 (2001) ("Ideally, under this view, a patent should be given for an invention only if the invention would not have been developed but for the patent. If the claimed invention would have been developed, commercialized, and disclosed even without a patent, then granting or enforcing a patent would make little sense.") (footnote omitted); Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 HIGH TECH. L.J. 1 (1992); Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CAL. L. REV. 803 (1988); Cecil D. Quillen, Jr., *Proposal for the Simplification and Reform of the United States Patent System*, 21 AIPLA Q. J. 189, 204 (1993).

[14] 35 U.S.C. § 103(a) (2000).

> nonobviousness of the subject matter is determined. Such 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. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.[15]

The Supreme Court further explained that "secondary evidence" of (non)obviousness (such as commercial success, long felt but unsolved needs, failure of others) "may . . . serve to 'guard against slipping into use of hindsight,' and to resist the temptation to read into the prior art the teachings of the invention in issue."[16]

In exercising appellate review over evaluations of inventions for (non)obviousness, the Federal Circuit has shown special concern with preventing the PTO and courts from slipping into improper hindsight analysis. This is a legitimate concern. Hindsight bias is a pervasive problem in the administration of a legal rule that calls for hypothetical ex ante evaluations and predictions by a trier who knows what happened ex post.[17] Gregory Mandel has argued on the basis of his own recent empirical work that (non)obviousness determinations are especially likely to be distorted by hindsight bias.[18]

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[15] 383 U.S. at 17–18 (citations omitted).

[16] 383 U.S. at 36 (citations omitted).

[17] There is a rich literature on the topic. For an early recognition of the problem, see Baruch Fischhoff, *Hindsight ≠ Foresight: The Effect of Outcome Knowledge on Judgment Under Uncertainty*, 1 J. EXPERIMENTAL PSYCHOL: HUM. PERCEPTION & PERFORMANCE 288 (1975). For more recent analyses with attention to implications for the legal system, see Jeffrey J. Rachlinski, *A Positive Psychological Theory of Judging in Hindsight*, 65 U. CHI. L. REV. 571 (1998); Kim A. Kamin & Jeffrey J. Rachlinski, *Ex Post ≠ Ex Ante: Determining Liability in Hindsight*, 19 LAW & HUM. BEHAV. 89 (1995) and sources cited therein; and Susan J. LaBine & Gary LaBine, *Determinations of Negligence and the Hindsight Bias*, 20 LAW & HUM. BEHAV. 501 (1996) and sources cited therein.

[18] See Mandel I and Mandel II, *supra* note 9. Mandel presented different groups of first-year law students with two hypothetical scenarios, including prior art references and a problem to be solved, and asked them whether the solution to the problem would have been obvious to a person having ordinary skill in the art. Half of each group of students was further told that the problem had been solved, and the solution was revealed to them. Students who had seen the solution (the hindsight group) were far more likely to respond that a solution was obvious than those who did not have this information (the foresight group). For the first scenario, 76% of the students in the hindsight group responded that a solution would have been obvious, and only 24% of those in the foresight group so responded. For the second scenario, 59% of the students in the hindsight group responded that a solution would have been obvious, and only 23% of those who had not seen the solution responded it would have been obvious. An interesting further result that Mandel reports but does not discuss is that the spread between the foresight and hindsight respondents in their perceptions of the likelihood that the hypothetical inventor would solve the problem suggests a much smaller gap between the two groups. Asked to quantify this likelihood on a scale of one to seven, with seven indicating that it was extremely likely that the inventor would achieve the invention, the mean responses for the first scenario were 4.40 in the foresight group and 5.41 in the hindsight group, and the

It is worth noting, however, that resort to hindsight in analyzing (non)obviousness is not simply a regrettable and inadvertent byproduct of cognitive limitations. Hindsight analysis is built into the obviousness inquiry as framed by Congress and elaborated by the Supreme Court. Although section 103(a) sets the time frame for the hypothetical analysis in the past—"at the time [the invention] was made"—it also directs the evaluator to consider the ex post state of the world in making this evaluation. The evaluation is to focus on "the [invention] as a whole" and to consider "the differences between the subject matter sought to be patented and the prior art."[19] This analysis is only possible ex post, when the evaluator knows what the invention as a whole is and can compare it to the prior art. The statutory analysis thus demands the use of a hindsight perspective. Moreover, the palliative against the hindsight bias endorsed by the Supreme Court in *Graham v. John Deere*—consideration of secondary evidence—involves further use of ex post evidence. Although some forms of secondary evidence (e.g., failure of others, long-felt but unsolved need) may be observed ex ante, the most common form—commercial success—may only be observed ex post.[20]

The Federal Circuit has fortified the relevance of evidence of secondary considerations, sometimes substituting the term "objective evidence" and giving it pride of place in the analysis alongside the other primary factual inquiries identified by the Supreme Court in *Graham v. John Deere*.[21] It has characterized the ultimate determination of (non)obviousness as a question of law subject to plenary review on appeal, allowing itself to engage in active appellate review of obviousness determinations.[22] And in a further effort to guard against hindsight bias,

mean responses for the second scenario were 4.05 for the foresight group and 4.66 for the hindsight group. Mandel I, *supra* note 9, at 1406–10. Perhaps this reflects an appreciation on the part of the law student survey respondents that the inventor is likely to have greater skill in this arena than they themselves possess.

[19] 35 U.S.C. § 103(a) (2000).

[20] Professor Mandel surveyed nonobviousness decisions in the Federal Circuit and district courts July 2004–December 2005 and found forty-one decisions that analyzed secondary consideration evidence. The most common consideration in these decisions was commercial success, which was considered in 33% of the cases. Other secondary considerations noted in Mandel's data set that can only be considered ex post include unexpected results (13% of cases), copying of the invention (12%), skepticism toward the invention (6%), and acclamation by others in the field (5%). Mandel I, *supra* note 9, at 1463.

[21] Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966). *See, e.g.* Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983) (evidence of secondary considerations often "the most probative and cogent evidence in the record."). *But see* Pfizer, Inc. v. Apotex, Inc. 480 F.3d 1348, 1370 (Fed. Cir. 2007) (discounting under the heading of "secondary considerations" properties of claimed invention not present in structurally similar prior art compounds).

[22] Aktiebolaget Karlstads Mekaniska Werkstad & KMW v. U.S. Int'l Trade Comm'n, 705 F.2d 1565, 1575 (Fed. Cir. 1983). The Supreme Court opinion in *Graham v. John Deere Co.* was ambiguous on this point, although earlier decisions of the Court had generally treated the presence or absence of patentable invention as a

before holding a claimed invention obvious, the Federal Circuit has required an identified "teaching, suggestion, or motivation" that would lead a person having ordinary skill in the art to bridge the gap between the prior art and the invention.[23] This requirement forces the PTO and the courts to focus on the prior art and to articulate an evidentiary basis for a conclusion of obviousness rather than relying on peremptory intuitions and "common sense."[24]

As a formal matter, the Federal Circuit has consistently acknowledged that the necessary "suggestion" to extend or combine prior art need not be explicit in prior art references, but might instead be found in "the knowledge of one of ordinary skill in the art" or in "the nature of the problem [to be] solved."[25] But even when the suggestion is implicit, it must be supported by "particular findings" rather than "conclusory statements."[26] The Federal Circuit has sometimes chastised the PTO for invoking the high skill level[27] or even "common sense"[28] of a PHOSITA to explain why the differences between the prior art and the claimed invention would have been obvious, accusing it of having fallen into the "hindsight trap."[29]

The Federal Circuit appeared especially demanding in its standards for proof of motivation to combine references in its review of obviousness determinations of the PTO in a series of cases following the decision of the Supreme Court in *Dickinson v. Zurko*.[30] In that case the Supreme Court held that, in reviewing findings of fact by the PTO, the Federal Circuit must apply the less stringent standards of review set forth in the Administrative Procedure Act rather than the "clearly erroneous" standard of review that the Federal Circuit had been using.[31] Rather than increasing its deference to PTO rejections, the Federal Circuit seized upon the Administrative Procedure Act as further authority for its

question of fact, as had some circuit court decisions prior to the formation of the Federal Circuit. For a review of early Supreme Court cases on this question, see 2 DONALD S. CHISUM, CHISUM ON PATENTS § 5.04[3][a] (2007). *See also* Koppers Co. v. Foster Grant Co., 396 F.2d 370, 372 (1st Cir. 1968); Moore v. Shultz, 491 F.2d 294 (10th Cir. 1974).

[23] KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1730 (2007).

[24] *In re* Lee, 277 F.3d 1338 (Fed. Cir. 2002); *In re* Zurko, 258 F.3d 1379, 1385 (Fed. Cir. 2001).

[25] Beckson Marine, Inc. v. NFM, Inc., 292 F.3d 718, 728 (Fed. Cir. 2002); SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349 (Fed. Cir. 2000)

[26] *In re* Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000); *In re* Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999).

[27] *In re* Rouffet, 149 F.3d 1350, 1357–58 (Fed. Cir. 1998).

[28] *In re Lee*, 277 F.3d at 1344; *In re Zurko*, 258 F.3d at 1385.

[29] *In re Kotzab*, 217 F.3d at 1371; *In re Dembiczak*, 175 F.3d at 999.

[30] 527 U.S. 150 (1999).

[31] On remand, the Federal Circuit determined that the Board's conclusions were not only "clearly erroneous" but also "lack[ed] substantial evidence," and the change in standard of review therefore did not change the outcome of the case. *In re* Zurko, 258 F.3d at 1381, 1385.

requirement that the PTO adequately document the teaching, suggestion or motivation to select and combine references to render an invention obvious.[32] In requiring the PTO and the courts to document the basis for a conclusion of obviousness—including a TSM showing—in the evidentiary record, the Federal Circuit's approach has sometimes seemed as a practical matter to require documentary evidence of a sort that simply may not exist, even for the most obvious inventions.[33]

Yet in other decisions, the Federal Circuit backed away from such a rigid requirement. For example, in *Ruiz v. A.B. Chance Co.*, the Federal Circuit denied that its prior decisions "provide a rule of law that an express, written motivation to combine must appear in prior art references before a finding of obviousness," insisting that "this court has consistently stated that a court or examiner may find a motivation to combine prior art references in the nature of the problem to be solved. This form of motivation to combine evidence is particularly relevant with simpler mechanical technologies."[34] The Federal Circuit has sometimes affirmed rejections for obviousness despite gaps in tracing the chain of inferences that support an implied "suggestion,"[35] acknowledged that the scientific competence of examiners and administrative patent judges might equip them to draw informed inferences about motivation to combine references,[36] and recognized that the suggestion or motivation

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[32] *See, e.g., In re Lee*, 277 F.3d at 1342–44:

> The agency tribunal must set forth its findings and the grounds thereof, as supported by the agency record, and explain its application of the law to the found facts. . . . When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. . . . It must be based on objective evidence of record . . . Deferential judicial review under the Administrative Procedure Act does not relieve the agency of its obligation to develop an evidentiary basis for its findings. To the contrary, the Administrative Procedure Act reinforces this obligation.

[33] *See, e.g.*, Brown & Williamson Tobacco Corp. v. Philip Morris, Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000) ("This evidence [of TSM] may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. However, the suggestion more often comes from the teachings of the pertinent references. This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence.'" (citations omitted)).

[34] Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276 (Fed. Cir. 2004) (citations omitted).

[35] *See, e.g., In re* Huston, 308 F.3d 1267, 1280 (Fed. Cir. 2002) (noting that the Board's "conclusions are cryptic, but they are supported by the record.").

[36] *See, e.g., In re* Berg, 320 F.3d 1310, 1315 (Fed. Cir. 2003) ("As persons of scientific competence in the fields in which they work, examiners and administrative patent judges on the Board are responsible for making findings, informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art and the motivation those references would provide to such persons. Absent legal error or contrary factual evidence, those findings can establish a prima facie case of obviousness.").

to combine need not be expressly stated in the prior art, but may come from reasoning based on established scientific principles or legal precedent.[37] But each of these approaches for rejecting a claim requires "particular findings" grounded in objective evidence,[38] making it more costly for PTO to reject claims.

The PTO's unhappiness with the Federal Circuit's TSM jurisprudence is apparent in a brief of the Solicitor General in *KSR*, responding to a Supreme Court call for the views of the United States on the petition for certiorari.[39] In language that appears to have significantly influenced the Court, the Solicitor General argued that "[t]he Federal Circuit has transformed one means of establishing obviousness . . . — proof that the prior art provided a teaching, suggestion, or motivation for combining separate prior art references—into an inflexible requirement" with the effect of "extend[ing] patent protection to non-innovative combinations of familiar elements."[40] Although *KSR* presented an appeal from a court decision in an infringement action rather than an appeal from a PTO decision, the Solicitor General stressed the burdens the TSM approach imposes on the PTO:

> The Federal Circuit's test not only shunts cases to trial that should be resolved at summary judgment, but it also unduly restricts the ability of PTO to reject obvious patent applications. Congress vested PTO with "primary responsibility for sifting out unpatentable material." That responsibility, which requires technical expertise drawn from a wide variety of disciplines, places extraordinary burdens on patent examiners, particularly in light of the high volume of patent applications. . . . Section 103(a) plays a crucial role in filtering out non-innovative applications and focusing the examination efforts on substantial claims. . . . PTO's obviousness inquiry should not require an unnecessary search for evidence showing a particular suggestion, teaching, or motivation to make insubstantially innovative combinations of elements that are known in the prior art. PTO should instead be allowed to bring to bear its full expertise—including its reckoning of the basic knowledge and common sense possessed by persons in particular fields of endeavor—when making the predictive judgment whether an

[37] *See In re* Fine, 837 F.2d 1071, 1074–75 (Fed. Cir. 1988); *In re* Sernaker, 702 F.2d 989, 994–95 (Fed. Cir. 1983); *In re* Eli Lilly & Co., 902 F.2d 943, 945–46 (Fed. Cir. 1990). The case law is summarized for examiners in § 2144 of UNITED STATES PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE (2007), *available at* http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2144.htm.

[38] *In re* Kotzab, 217 F.3d 1365, 1370 (Fed. Cir. 2000) ("Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. Broad conclusory statements standing alone are not 'evidence.'" (citations omitted)).

[39] KSR Int'l Co. v. Teleflex, Inc., 546 U.S. 808 (2005).

[40] Brief of United States as Amicus Curiae at 9, KSR v. Teleflex, 127 S. Ct. 1727 (2007) (No. 04-1350).

> invention would have been obvious to a person of ordinary skill in the art.[41]

The Federal Circuit noticeably softened its TSM rhetoric while *KSR* was pending on appeal. Affirming a rejection for obviousness in *In re Kahn*,[42] the Federal Circuit underscored its deference to the findings of the PTO, noting that "the Board need only establish motivation to combine by a preponderance of the evidence to make its *prima facie* case" and that "[a]lthough a reasonable person might reach the opposite conclusion, there is far more than a 'mere scintilla' of evidence present from which a reasonable mind could find a motivation to combine."[43] In *Alza Corp. v. Mylan Laboratories, Inc.*[44] the Federal Circuit touted the flexibility of its TSM approach and its consistency with Supreme Court precedent:

> [O]ur approach has permitted us to continue to address an issue of law not readily amenable to bright-line rules, as we recall and are guided by the wisdom of the Supreme Court in striving for a "practical test of patentability." . . . [U]nder our non-rigid "motivation-suggestion-teaching" test, a suggestion to combine need not be found in the prior art.[45]

In *Dystar Textilfarben GMBH & Co. v. C.H. Patrick Company*,[46] the Federal Circuit complained that critics[47] had quoted its TSM decisions out of context, reviewed the decisions at length, and concluded:

> It is difficult to see how our suggestion test could be seen as rigid and categorical given the myriad cases over several decades in which panels of this court have applied the suggestion test flexibly. . . . Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense.[48]

Empirical investigations of (non)obviousness decisions by different legal scholars offer mixed reviews of the Federal Circuit's (non)obviousness jurisprudence on the ground. Glynn Lunney, in a review of all appellate decisions in patent infringement cases during

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[41] *Id.* at 17–18 (citations omitted).

[42] 441 F.3d 977 (Fed. Cir. 2006).

[43] *Id.* at 989 (emphasis in original).

[44] 464 F.3d 1286, 1291 (Fed. Cir. 2006).

[45] *Id.* at 1291, 1294.

[46] 464 F.3d 1356 (Fed. Cir. 2006).

[47] *See, e.g.*, FED. TRADE COMM'N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 28 (2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf; NAT'L RESEARCH COUNCIL, A PATENT SYSTEM FOR THE 21ST CENTURY 89 n. 19 (Nat'l Acad. Press 2004), *available at* http://www.nap.edu/catalog.php?record_id=10976.

[48] *Dystar*, 464 F.3d at 1367 (emphasis in original).

eight two-year periods between 1944 and 1995,[49] found a sharp and steady decline in the percentage of patents held invalid, from a high of 63.79% between 1975 and 1976, to a low of 25% in the final period under study, 1994 to 1995, tending to confirm the Federal Circuit's reputation as a pro-patent court.[50] Lunney found an even more dramatic decline in the Federal Circuit era in the percentage of decisions in which invalidity was based on obviousness. During the six two-year periods prior to the formation of the Federal Circuit, obviousness accounted for a majority of appellate holdings of patent invalidity, representing between 66.67% and 79.49% of the cases reviewed. After the creation of the Federal Circuit, this number fell sharply to 50% of the cases between 1984 and 1985, and 20% of the cases between 1994 and 1995.[51] These numbers suggest that (non)obviousness has played a diminishing role in appellate judgments in the Federal Circuit era.

John Allison and Mark Lemley examined all reported written opinions of final decisions on patent validity, whether in district courts or in the Federal Circuit, during the period 1989–1996.[52] They found that courts upheld validity 54% of the time, and that when patents were held invalid, obviousness was the reason 42% of the time. Although their data were broadly consistent with Lunney's, Allison and Lemley did not examine changes over the course of the time period under study.

Sean McEldowney compared district court decisions on (non)obviousness before and after the creation of the Federal Circuit[53] and found a significant decline in the likelihood that a patent would be held invalid if the issue of (non)obviousness was adjudicated, from 55% in the period 1970–1975 to 31% in the period 1995–2000.[54] McEldowney found an even more remarkable decline in the number of cases addressing the (non)obviousness issue, with district courts reaching the question of obviousness for sixty-four patents in 1970 and only twenty patents in 2000, although the number of patents issued and infringement suits filed more than doubled between 1970 and 2000.[55] These results

[49] Glynn S. Lunney, Jr., *E-Obviousness*, 7 MICH. TELECOMM. & TECH. L. REV. 363, 370–75 (2001).

[50] *Id.* at 371–72. Earlier studies had also indicated that patents were more likely to be held valid (or not invalid, in the Federal Circuit's preferred locution) after the creation of the Federal Circuit than before. *Compare* GLORIA K. KOENIG, PATENT INVALIDITY: A STATISTICAL AND SUBSTANTIVE ANALYSIS § 4.02, 4–19 (rev. ed. 1980) (indicating that from 1953 to 1978 courts upheld the validity of patents 42% of the time) *with* John R. Allison & Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 AIPLA Q. J. 185, 205 (1998) (finding that from 1989 through 1996 courts upheld the validity of patents 54% of the time).

[51] Lunney, *supra* note 49 at 373–75.

[52] Allison & Lemley, *supra* note 50, at 185.

[53] Sean M. McEldowney, *New Insights on the "Death" of Obviousness: An Empirical Study of District Court Obviousness Opinions*, 2006 STANFORD TECH. L. REV. 4, ¶ 3 (2006).

[54] *Id.* figs. 1–2, ¶¶ 35–36.

[55] *Id.* tbl. 3, ¶¶ 37–38.

support Lunney's conclusion that (non)obviousness has declined in significance during the Federal Circuit era.

Other empirical scholars have presented different data to defend the Federal Circuit's nonobviousness jurisprudence against its critics. Lee Petherbridge and Polk Wagner, in a study of Federal Circuit analyses of (non)obviousness between 1990 and 2005, found that the Federal Circuit affirmed the judgments of lower courts and the PTO on (non)obviousness approximately 65% of the time, a number that remained stable over the period under study and is significantly higher than rates of affirmance previously reported for other issues.[56] Moreover, they found that the Federal Circuit held the invention at issue to be obvious 57.8% of the time,[57] with similar results for mechanical, chemical, and biotechnology inventions, and that application of the TSM test had no apparent effect on the likelihood of affirmance and only modestly increased the likelihood of a conclusion of nonobviousness.[58]

Christopher Cotropia studied final decisions of the Federal Circuit on patent validity from 2002–2005 to test whether the Federal Circuit has reduced the standard of nonobviousness through its TSM approach.[59] He found that the Federal Circuit was more likely to affirm a lower court finding of obviousness, with an affirmance rate of 62.5%, than a lower court finding of nonobviousness, for which the affirmance rate was 48.15%, although the difference was not statistically significant.[60] He also found that, ignoring cases in which the Federal Circuit vacated the judgment below, the percentage of patents that the Federal Circuit held nonobvious (56.06%) was only slightly higher than the percentage it held obvious (43.93%).[61] The Federal Circuit affirmed determinations of obvious 86.79% of the time, calling into question the view that the Federal Circuit's (non)obviousness jurisprudence has made it difficult to reject obvious claims. In appeals from district court decisions, the TSM test prompted a determination of nonobvious, or vacation of a finding of obvious, for twenty-five patents, compared to fifty-four patents where it played no role.[62] In appeals from the PTO, the TSM test led the Federal

[56] Lee Petherbridge & R. Polk Wagner, *The Federal Circuit and Patentability: An Empirical Analysis of the Law of Obviousness*, 85 TEXAS L. REV. 2051, 2079 (2007) (comparing data to results of Chu and Moore). *See* Christian A. Chu, *Empirical Analysis of the Federal Circuit's Claim Construction Trends*, 16 BERKELEY TECH. L.J. 1075, 1098 (2001) (finding that the Federal Circuit's reversal rate for claim construction was approximately 50%); Kimberly A. Moore, *Are District Court Judges Equipped to Resolve Patent Cases?*, 15 HARV. J.L. & TECH. 1, 11 (2001) (finding that Federal Circuit's reversal rate for claim construction was approximately 33%).

[57] Petherbridge & Wagner, *supra* note 56, at 2087.

[58] *Id.* at 2091–93.

[59] Christopher A. Cotropia, *Nonobviousness and the Federal Circuit: An Empirical Analysis of Recent Case Law*, 82 NOTRE DAME L. REV. 911 (2007).

[60] *Id.* at 931–33.

[61] *Id.* at 934.

[62] *Id.* at 944–45.

Circuit to rule in favor of the patent applicant in slightly less than 10% of the cases.[63]

The divergent conclusions drawn by the authors of these studies are puzzling, and suggest that the authors' methodologies may involve more judgment and interpretation than they claim. Evidently, the many decisions of the Federal Circuit may be aggregated in different ways to support different claims. The Supreme Court recognized that the Federal Circuit's (non)obviousness jurisprudence is not uniform in its *KSR* opinion, acknowledging that the Federal Circuit may have applied its TSM test less rigidly in other cases, although noting that the other decisions "are not now before us and do not correct the errors of law made by the Court of Appeals in this case."[64] Even if not relevant to the immediate task before the Supreme Court in *KSR*, the complex (non)obviousness jurisprudence of the Federal Circuit is surely a topic worthy of the consideration of legal scholars. Perhaps these varied decisions cannot be characterized in a meaningful way by coding and aggregating the cases without examining more closely what they do and what they say. But before embarking upon that analysis, I first examine the *KSR* decision itself more closely.

III. *KSR* AND THE DISAPPROVAL OF RIGID FORMULAS

Followers of the Federal Circuit's (non)obviousness jurisprudence are divided on whether the decision of the Supreme Court in *KSR* is (a) a radical departure from the Federal Circuit's approach, or (b) unlikely to change much.[65] What makes the decision seem radical is that the Court turned just about every move that the Federal Circuit has made to standardize and formalize the analysis of (non)obviousness on its head. What makes it seem unlikely to change much is that, in the end, the Court left the Federal Circuit with considerable latitude to apply the (non)obviousness standard as it wishes, so long as it does not do so in a rigid manner. The Court did not even disapprove of the TSM approach, so long as it is used flexibly. Moreover, the Court endorsed the Federal Circuit's characterization of the ultimate determination of (non)obviousness as a question of law, leaving the Federal Circuit with considerable room for active appellate review of the issue.

The invention at issue in *KSR* was an adjustable pedal assembly for an automobile that could accommodate drivers of different heights. The claimed assembly incorporated an electronic control sensor mounted on a support and responsive to a pivot, with the pivot remaining in a constant position while the pedal could be adjusted forward and

[63] *Id.* at 946–47.

[64] KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1743 (2007).

[65] *See* Posting of Peter Lattman to Wall Street Journal Law Blog, *KSR v. Teleflex: The Supreme Court's Big Patent Ruling*, http://blogs.wsj.com/law/2007/05/01/ksr-v-teleflex-the-supreme-courts-big-patent-ruling (May 1, 2007, 8:07 EST).

backward. Finding each of the claim limitations in the prior art, and concluding that a person having ordinary skill in the art would have been motivated to combine the elements, the trial court awarded summary judgment of invalidity to KSR. The Federal Circuit reversed, vacated and remanded in a nonprecedential opinion,[66] holding that the district court had failed to make specific enough findings as to the teaching, suggestion, or motivation to combine the elements of the invention.[67] KSR appealed, and the Supreme Court reversed in a unanimous opinion.

The Supreme Court largely ignored a quarter century of Federal Circuit decisions attempting to formalize the (non)obviousness inquiry, turning instead to its own much earlier decisions that "set forth an expansive and flexible approach."[68] The Justices reiterated the continuing vitality of the Supreme Court's ancient skepticism towards patents that combine elements found in the prior art,[69] a skepticism that stands in contrast to the Federal Circuit's insistence on finding a teaching, suggestion or motivation to combine elements found in different prior art references before declaring a combination obvious.[70] They repeatedly approved of resort to "common sense" in evaluating an invention for obviousness,[71] in contrast to the Federal Circuit's at least occasional suspicion of common sense as camouflage for lack of evidence

[66] Teleflex, Inc. v. KSR Int'l. Co., 119 Fed. App'x 282 (Fed. Cir. 2005). As it does in all non-precedential opinions, the Federal Circuit recited in all capital letters at the beginning of the opinion: "This case was not selected for publication in the Federal Reporter. NOTE: Pursuant to Fed.Cir.R. 47.6, this order is not citable as precedent." *Id.*

[67] *Id.* at 286–88.

[68] *KSR Int'l Co.*, 127 S. Ct. at 1739.

[69] *Id.* at 1739 ("Neither the enactment of § 103 nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art.").

[70] *E.g., In re* Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (citations omitted):

> As this court has stated, 'virtually all [inventions] are combinations of old elements.' Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.' To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

[71] The Court used the phrase "common sense" five times in its opinion, always approvingly. *KSR Int'l Co.*, 127 S. Ct. at 1741–43.

and hindsight bias.[72] They explicitly told the Federal Circuit that fear of the hindsight bias is no excuse for "[r]igid preventative rules that deny factfinders recourse to common sense."[73]

The Supreme Court repeatedly invoked "market forces" as tending to motivate improvements upon the prior art and therefore to make them obvious.[74] By contrast, when the Federal Circuit takes note of parallel research efforts by others in the same industry to solve a problem, it generally counts it as evidence that the invention must have been nonobvious.[75] To the Federal Circuit, if market forces make a solution to a technological problem obviously desirable, yet nobody figured out how to do it before the patentee, that suggests that the invention was not obvious. To the Supreme Court, market demand for the invention makes it likely that the problem will be solved in the ordinary course of events by persons of ordinary skill with or without the efforts of the patentee.[76]

The Supreme Court disapproved of the Federal Circuit's focus on the problem that the patentee was trying to solve as the point of departure for figuring out whether the invention was obvious, preferring instead an "objective" approach that asks whether the claimed invention was likely to come about as the obvious solution to *any* known problem in light of the prior art.[77]

They questioned the Federal Circuit's standard bromide—not even relevant in the facts of *KSR*—that an invention may be "obvious to try"

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[72] *E.g.*, *In re* Lee, 277 F.3d 1338, 1344–45 (Fed. Cir. 2002); *In re* Zurko, 258 F.3d 1379, 1385 (Fed. Cir. 2001).

[73] *KSR Int'l Co.*, 127 S. Ct. at 1742–43.

[74] *See id.* at 1740 ("When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one."); *id.* at 1740–41 ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue."); *id.* at 1741 ("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."); *id.* at 1742 ("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."); *id.* at 1744 ("There then existed a marketplace that created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance.").

[75] *See, e.g.*, Gillette Co. v. S.C. Johnson & Son Inc., 919 F.2d 720, 725–26 (Fed. Cir. 1990) (the fact that defendant's researchers were pursuing similar research but did not introduce a similar product until after plaintiff's invention indicates that the invention was nonobvious rather than obvious).

[76] *KSR Int'l Co.*, 127 S. Ct. at 1741–42.

[77] *Id.* at 1741–42.

and still nonobvious.[78] The "obvious to try" limitation on nonobviousness analysis comes into play when the prior art leaves substantial uncertainty as to whether a possible solution to a problem would work, leaving the inventor to sort through many possibilities without any reasonable expectation of success.[79] The Federal Circuit has repeatedly held that such a solution, although obvious to try, is still nonobvious, and gratuitously recited this principle in its *KSR* opinion,[80] prompting the Supreme Court to observe that if an invention is obvious to try with an expectation of success, it is probably obvious.[81]

Finally, the Supreme Court turned the Federal Circuit's concern about hindsight on its head. For the Federal Circuit, the hindsight bias is something that leads to incorrect determinations of obviousness for inventions that, if properly evaluated as of the time they were made in light of the prior art alone, would in fact be seen as nonobvious. But the Supreme Court saw the Federal Circuit as trapped by a different hindsight bias that cuts the other way. The Supreme Court cautioned against the use of hindsight to document the inadequacies of the prior art, suggesting that the avoidance of hindsight does not always favor patent validity.[82] Just as it is improper to use hindsight against the patentee by using the patentee's combination as a guide to the prior art, it is improper to use hindsight in favor of the patentee by using the invention to dismiss the prior art as inadequate. To the Supreme Court, hindsight bias is not a one-way ratchet.

In sum, the Supreme Court's analysis in *KSR* suggests sharp differences with the Federal Circuit on just about every tool that the Federal Circuit has deployed over the years in its efforts to standardize and formalize the (non)obviousness inquiry, to guard against the hindsight bias, and to document the basis for rejections and invalidity holdings explicitly in the record.

On the other hand, apart from disapproving of rigidity, the *KSR* decision does little to constrain the Federal Circuit in its analysis of (non)obviousness. Consistent with the Federal Circuit's insistence that the basis for conclusions of obviousness be documented in the record, the Supreme Court in *KSR* stated that the analysis should be made explicit in order to facilitate review.[83] The Supreme Court did not even prohibit the use of teaching, suggestion or motivation as part of the (non)obviousness inquiry, so long as it is not done in a rigid manner that

[78] *Id.* at 1742.

[79] *See e.g.*, *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

[80] Teleflex, Inc. v. KSR Int'l. Co., 119 Fed. App'x 282, 289 (Fed. Cir. 2005).

[81] *KSR Int'l Co.*, 127 S. Ct. at 1742.

[82] *Id.* at 1745 ("Teleflex may have made a plausible argument that [the prior art] Asano [device] is inefficient as compared to Engelgau's preferred embodiment, but to judge Asano against Engelgau would be to engage in the very hindsight bias Teleflex rightly urges must be avoided").

[83] *Id.* at 1741 (citing *In re* Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)).

prevents consideration of "the inferences and creative steps that a person of ordinary skill in the art would employ."[84]

Importantly, the Supreme Court adopted the Federal Circuit's characterization of the ultimate issue of obviousness as a question of law,[85] subject to plenary review on appeal. In *Graham v. John Deere*, the Supreme Court had left this characterization somewhat ambiguous, stating that "[w]hile the ultimate question of patent validity is one of law . . . the § 103 condition . . . lends itself to several basic factual inquiries."[86] In a short *per curiam* opinion in *Dennison Manufacturing Co. v. Panduit Corp.*, the Court revisited this language, vacating and remanding a decision by the Federal Circuit that had overturned a trial court finding of invalidity for obviousness without holding that the trial court's findings were clearly erroneous as required by Rule 52 of the Federal Rules of Civil Procedure.[87] The Supreme Court lamented that "we lack the benefit of the Federal Circuit's informed opinion on the complex issue of the degree to which the obviousness determination is one of fact," suggesting that it regarded the issue as unresolved.[88] On remand, the Federal Circuit stated its view that the conclusion as to obviousness is one of law based on subsidiary fact-findings.[89]

In *KSR*, the Court cited its own decision in *Graham* for the proposition that the ultimate judgment of obviousness is a legal determination, without noting any prior ambiguity.[90] Given the procedural posture of the *KSR* case, in which the Federal Circuit had reversed a district court's grant of summary judgment of invalidity, the Court had to conclude that (non)obviousness is a question of law in order to reach the merits itself and reinstate summary judgment for the defendant.[91] If the ultimate judgment was a question of fact, it would have been difficult, in the face of conflicting expert testimony, to maintain that there was no genuine issue of material fact for trial. In order to reverse the Federal Circuit, the Supreme Court thus had to characterize the ultimate issue as a question of law.

But if the ultimate determination of (non)obviousness is a question of law, for all practical purposes the issue will continue to belong to the Federal Circuit. In theory, of course, the legal rulings of the Federal

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[84] *Id.*

[85] *Id.* at 1745.

[86] 383 U.S. 1, 17 (1966).

[87] 475 U.S. 809 (1986).

[88] *Id.* at 811.

[89] Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566 (Fed. Cir. 1987). The Federal Circuit noted that *Graham v. John Deere* has been widely interpreted as holding that the conclusion as to obviousness is a question of law, "because the validity issue in *Graham* turned on that answer and because of what the Court did in *Graham*. It disagreed with conclusions reached below, did not remand, described no finding as 'clearly erroneous,' and did not mention Rule 52(a)." *Id.* at 1567.

[90] KSR Int'l Co., 127 S. Ct. at 1745 (2007).

[91] Teleflex, Inc. v. KSR Int'l. Co., 119 Fed. App'x 282, 290 (Fed. Cir. 2005).

Circuit are subject to review by the Supreme Court, and the Supreme Court can review as many decisions of the Federal Circuit as it feels necessary in order to ensure that (non)obviousness doctrine remains "expansive and flexible."[92] But whether they are characterized as questions of law or questions of fact, determinations of (non)obviousness will remain difficult and technical. It is hard to imagine the Supreme Court reviewing these determinations on more than a sporadic basis. So long as the Federal Circuit shows a modicum of respect for the Supreme Court's teachings,[93] it seems unlikely that the Supreme Court will seek out opportunities to revisit the issue. It is easier to observe how the Federal Circuit writes its opinions than it is to monitor how it actually decides cases.

I return to the jurisprudence of the Federal Circuit to examine more closely what it says and does in evaluating the (non)obviousness of chemical and pharmaceutical inventions.

IV. CHEMICAL OBVIOUSNESS: FROM FLEXIBILITY TO RIGID FORMALISM, WITH LIBERAL CONSIDERATION OF POST-INVENTION EVIDENCE

Although in principle the (non)obviousness standard is the same across all fields of technology, many lower court decisions have elaborated special rules for evaluating the (non)obviousness of "chemical" inventions. Most Supreme Court decisions considering the (non)obviousness requirement (or its pre-1952 antecedent, the "invention" requirement) have involved relatively simple mechanical inventions that the Court deemed unpatentable. Perhaps this reflects a selection bias in granting certiorari in favor of cases about technology that the Justices can understand. A rare Supreme Court case upholding the (non)obviousness of an invention was *United States v. Adams*, a case involving a battery that made use of a chemical reaction.[94] Although it did not articulate a different standard for evaluating chemical inventions, in concluding that the invention was (non)obvious and patentable the Court noted the unpredictability of the results of the chemical reaction, even though it combined old elements that were each separately disclosed in the prior art.[95]

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[92] *KSR Int'l Co.*, 127 S. Ct. at 1739.

[93] The Federal Circuit may be off to a poor start in showing its respect for *KSR*. In three post-*KSR* (non)obviousness cases the Federal Circuit has not even cited *KSR*. Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263 (Fed. Cir. 2007); Daiichi Sankyo, Co. v. Apotex, Inc., 501 F.3d 1254 (Fed. Cir. 2007); Frazier v. Layne Christensen Co., 239 Fed. App'x 604 (Fed. Cir. 2007).

[94] United States v. Adams, 383 U.S. 39 (1966).

[95] *Id.* at 51–52. *But cf.* Mandel Bros, Inc. v. Wallace, 335 U.S. 291 (1948) (holding invalid a patent on an improved antiperspirant that used urea to neutralize acidity on ground that results would have been predictable to chemists).

A long line of cases from the Federal Circuit and the CCPA have developed a distinct approach to evaluating the (non)obviousness of chemical inventions. One notable feature of these cases is their embrace of a hindsight perspective. In contrast to the concern behind the TSM test—that inventions will appear more obvious in hindsight than they in fact would have been at the time they were made—a recurring concern in chemical cases is that inventions that appeared obvious ex ante can be more accurately seen in hindsight to have surprising and nonobvious features that make them worthy of patent protection. In a series of decisions, the CCPA called the PTO to task for failing to consider such post-invention evidence and for focusing too rigidly on the ex ante obviousness of chemical structure in evaluating the patentability of new chemicals.

Consideration of post-invention evidence responds to the realities of research in the chemical arts. Many new chemicals are created by making small changes in prior art molecules. These changes may be conventional in nature, readily contemplated and executed by chemists of ordinary skill. Nonetheless, an obvious variation on a previously known chemical may have surprising properties. Some properties of new chemicals are either predictable or immediately apparent upon synthesis. But often it takes time to determine the properties of a new chemical through testing and observation that cannot take place until after the chemical is in hand. To the extent that (non)obviousness resides in differences in properties between a new chemical and structurally similar chemicals in the prior art, the evaluation must await observation of these properties.

Consider the important opinion of Judge Rich for the CCPA in *In re Papesch*.[96] The patent applicant claimed novel triethyl compounds that were structurally similar to trimethyl compounds in the prior art, but comparative tests performed on the new and old chemicals showed that the claimed compounds were active anti-inflammatory agents while the prior art compounds lacked this property. The examiner rejected the claims on the ground that the new molecules differed from the prior art only by substituting "obvious homologs of the methyl groups shown in identical positions in the reference compound and the method of preparation is substantially the same."[97] The examiner found the difference in properties "interesting but irrelevant" to the compound claims, noting that "if an invention is present, it resides in the use of the claimed compounds as anti-inflammatory agents and should be claimed as such."[98] The Patent Office Board of Appeals affirmed, noting that, given the obviousness "to the chemist" of the claimed compounds in light of the prior art, the showing of new pharmacological properties was akin to "secondary evidence" of (non)obviousness that might be useful in case

[96] 315 F.2d 381 (C.C.P.A. 1963).

[97] *Id.* at 382.

[98] *Id.* at 383–84 (quoting from examiner's final rejection).

of doubt, but was insufficient to override the clear showing of obviousness in this case based on chemical structure.[99]

Judge Rich reversed in an opinion that preferred actual hindsight evidence of nonobviousness over ex ante speculation:

> If that which appears, at first blush, to be obvious though new is shown by evidence *not* to be obvious, then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall.[100]

The "evidence" that could show that a new chemical that appears "at first blush" to be obvious is in fact nonobvious was evidence of "unexpected advantageous properties"—anti-inflammatory activity in the case of the molecules claimed by Papesch. Judge Rich did not purport to announce a new principle, but summed up a review of prior cases as follows:

> Where what we may call the apparent obviousness of the compound (including its properties) was overcome by evidence of unexpected advantageous properties the claim to it was held patentable; but where no such properties were shown to exist it remained an obvious compound with obvious properties.[101]

The reasoning behind the prior decisions varied, with some cases resting on the lack of suggestion or motivation to make the claimed compounds given the failure of the prior art to predict their unexpected properties.[102] But Judge Rich did not so characterize the case before him, perhaps because other useful properties of the prior art compounds would have been sufficient to motivate the creation of homologs. Instead, he treated the surprising anti-inflammatory properties as new evidence revealing the claimed compounds to be less similar to the prior art compounds than one might have expected ex ante. Judge Rich declined to distinguish between the obviousness of the compounds themselves and the nonobviousness of their properties, famously observing:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to *identify* what is being patented, as the metes and bounds of a deed identify a plot of land, the *thing* that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of

[99] *Id.* at 385–86 (quoting from board opinion).

[100] *Id.* at 386–87 (emphasis in original)

[101] *Id.* at 389.

[102] *Id.* at 389–90 (discussing *In re* Bergel, 292 F.2d 955 (C.C.P.A. 1961) and *In re* Larsen, 292 F.2d 531 (C.C.P.A. 1961).

> the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.[103]

Judge Rich commended the Board for ignoring the examiner's argument that, if it is the properties rather than the structure of the claimed compound that are nonobvious, the applicant should be limited to claiming a process utilizing the newly discovered property rather than getting a product claim to the compound itself.[104] He dismissed the argument that the claimed and prior art compounds, given their structural similarity, presumably have many properties in common, noting: "*Presumably* they do, but presumption is all we have here."[105] He noted pragmatically that "product claims . . . . have well-recognized advantages to those in the business of making and selling compounds, in contrast to process-of-use claims, because competitors in the sale of compounds are not generally users."[106] He thus rejected the rigid approach of the PTO with its focus on chemical formulae in favor of pragmatic flexibility, including unabashed reliance on hindsight evaluation of evidence that was not available at the time the invention was made, in order to give business firms the patent claims they needed to develop molecules with new uses.

The Federal Circuit revisited some of the same issues in its 1990 en banc decision in *In re Dillon*.[107] The *In re Dillon* opinion, although consistent with *In re Papesch*, reveals greater concern with clarifying and formalizing the correct analytical approach to (non)obviousness determinations, with specifying formal burdens of proof and the kind of evidence that will meet those burdens, and with maintaining the distinction between product and process claims that Judge Rich preferred to gloss over in *In re Papesch*.

The inventor in *In re Dillon* discovered that tetra-orthoester compounds, when added to hydrobcarbon fuels, will reduce emissions of soot during combustion of the fuel. She claimed a composition of hydrocarbon fuel plus enough tetra-orthoester "to reduce the particulate emissions from the combustion of the hydrocarbon fuel."[108] The prior art included tetra-orthoester compounds, but did not disclose their combination with hydrocarbon fuel, nor did it suggest their use to reduce particulate emissions from fuel combustion. The prior art did, however, describe compositions that combined hydrocarbon fuels with structurally similar tri-orthoesters for the different purpose of

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[103] *Id.* at 391 (emphasis in original).
[104] *Id.*
[105] *Id.* (emphasis in original).
[106] *Id.*
[107] 919 F.2d 688 (Fed. Cir. 1990)
[108] *Id.* at 690 (reciting Claim 2).

"dewatering" the fuels.[109] The Board affirmed rejection of the claims for obviousness, noting that there was a reasonable expectation that the tri- and tetra-orthoester fuel compositions would have similar properties given their structural similarities. In the Board's view, this made the tetra-orthoester fuel compositions prima facie obvious, shifting the burden to the applicant to show unexpected or surprisingly advantageous properties for the claimed compositions that the prior art did not share.[110] Dillon failed to make this showing, and in fact showed quite the opposite. Her original patent application claimed tri-orthoester fuel compositions as well as tetra-orthoester fuel compositions, and included data showing equivalent activity for both compositions in reducing particulate emissions.[111]

But Dillon's own patent application was not in the prior art, and Dillon argued that her own disclosure should not be used against her to show that her invention was obvious. The Federal Circuit, evidently troubled by this argument, did not rest on the comparative data from her specification in its analysis.[112] The Federal Circuit panel that first considered Dillon's appeal reversed the PTO, holding that "when the claimed subject matter is a new chemical compound or composition, a *prima facie* case of obviousness is not deemed made unless both (1) the new compound or composition is structurally similar to the reference compound or composition and (2) there is some suggestion or expectation in the prior art that the new compound or composition will have the same or a similar utility as that discovered by the applicant."[113]

Rehearing the case en banc, the Federal Circuit withdrew the panel opinion and affirmed the rejection. Because Dillon had not chosen to argue the patentability of her process claims separately, the Federal Circuit only considered the composition claims. Judge Lourie's opinion for the en banc majority nonetheless suggested that this distinction mattered, in striking contrast to Judge Rich's comment in *Papesch* that the Board correctly ignored the distinction.[114] Responding to Dillon's argument that none of the prior art references disclosed or suggested her new use for the compositions, Judge Lourie noted that "the composition claims are not limited to this new use; *i.e.*, they are not

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[109] *Id.* at 691.

[110] *Id.*

[111] *Id.*

[112] *Id.* at 694:

> While we caution against such a practice, it is clear to us that references by the PTO to the comparative data in the patent application were not employed as evidence of equivalence between the tri- and tetra-orthoesters; the PTO was simply pointing out that the applicant did not or apparently could not make a showing of superiority for the claimed tetra-ester compositions over the prior art tri-ester compositions.

[113] *In re* Dillon, 892 F.2d 1554, 1560 (Fed. Cir. 1989), *opinion withdrawn by rehearing en banc*, 919 F.2d 688 (Fed. Cir. 1990).

[114] *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

physically or structurally distinguishable over the prior art compositions except with respect to the orthoester component."[115] Focusing upon the compositions themselves, Judge Lourie found the prior art sufficiently close to make them prima facie obvious:

> We believe that the PTO has established, through its combination of references, that there is a sufficiently close relationship between the tri-orthoesters and tetra-orthoesters . . . in the fuel oil art to create an expectation that hydrocarbon fuel compositions containing the tetra-esters would have similar properties, including water scavenging, to like compositions containing the tri-esters, and to provide the motivation to make such new compositions.[116]

The PTO, having shown both structural similarity between the claimed and prior art compositions and motivation in the prior art to make the claimed compositions, established a prima facie case of obviousness, shifting the burden to the applicant to rebut that prima facie case with further evidence:

> Such rebuttal or argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument or presentation of evidence that is pertinent. 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, but it is also clear that the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a *prima facie* case.[117]

A comparison of the Federal Circuit's opinion in *In re Dillon* with the CCPA's opinion in *In re Papesch* reveals on the part of the Federal Circuit a greater inclination towards formalism, more careful attention to the mechanics of proof, and a sharper focus on the differences between the invention as claimed and the prior art, as well as renewed attention to the difference between product and process claims. It does not, however,

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[115] *In re Dillon*, 919 F.2d at 692.

[116] *Id.*

[117] *Id.* at 692–93 (citations omitted) (emphasis in original). The en banc majority was unmoved by the argument that the prior art references did not make the invention obvious because they did not relate to the problem Dillon confronted, noting that the composition claims were not limited to such a use, but left open the possibility that Dillon might be entitled to process claims that focused more narrowly on the problem of reducing particulate emissions. *Id.* at 695 ("We make no judgment as to the patentability of claims that Dillon might have made and properly argued to a method directed to the novel aspects of her invention, except to question the lack of logic in a claim to a method of reducing particulate emissions by combusting."). For an interesting analysis of *In re Dillon* as a rare example of the use of the doctrine of inherency in nonobviousness analysis, see Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371, 395–400 (2005).

reveal either a greater bias toward patent validity or a greater concern with avoiding hindsight evaluations. Both courts invite consideration of post-invention evidence to compare the properties of the invention with those of the prior art. Although the Federal Circuit was careful not to rely on Dillon's own disclosure to show that the undisclosed properties of the prior art were the same as the properties of the claimed invention, it was willing to place the burden of proof on Dillon to show that they were different. Because Dillon had failed to rebut the PTO's prima facie case of obviousness, she was unable to obtain a patent, even though the prior art did not disclose the properties that she demonstrated for the claimed invention.

Concern about the hindsight bias features more prominently in cases admonishing the PTO and district courts that an invention that is "obvious to try" may nonetheless be nonobvious if the prior art does not establish a reasonable expectation of success.[118] Although the principle that "obvious to try" is not enough to defeat patentability is not limited to chemical obviousness, it has been particularly important in sustaining the patentability of chemical and biotechnology inventions.

The Federal Circuit elaborated upon the distinction between what is obvious and what is merely obvious to try in *In re O'Farrell*:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. 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. . . .
>
> 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.[119]

[118] *See, e.g.*, *In re* Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966) ("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.'").

[119] *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

In *O'Farrell*, where the prior art included an article by the inventors explicitly suggesting the invention and predicting success more than a year prior to their own patent filing date, the court concluded that the prior art did more than make the invention obvious to try.[120] But in other early biotechnology cases, the court was skeptical about whether there would have been a reasonable expectation of success when the prior art made inventions obvious to try.

In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*,[121] the Federal Circuit reversed a judgment holding invalid a patent on an immunometric "sandwich assay"[122] for detecting the presence of an antigen in fluid samples using monoclonal antibodies. The prior art disclosed similar sandwich assays using conventional polyclonal antibodies, as well as techniques for producing monoclonal antibodies. The Federal Circuit concluded that the prior art references were no more than "invitations to try monoclonal antibodies in immunoassays" that "do not suggest how that end might be accomplished."[123] In *In re Vaeck* the Federal Circuit reversed a rejection of claims to a chimeric gene capable of being expressed in cyanobacteria (blue-green algae) that linked a gene for an insecticidal protein from *Bacillus* bacteria with a promoter region effective to cause expression in a cyanobacteria host.[124] The prior art disclosed the expression of chimeric genes in cyanobacteria hosts, genes encoding insecticidal proteins expressed in *Bacillus*, and the advantages of expressing genes in recombinant hosts in order to obtain larger quantities of the gene product. The PTO concluded that this made the invention prima facie obvious, but the Federal Circuit reversed, asserting that "[t]he prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so."[125]

In each of these cases, the Federal Circuit asks whether the prior art provided both motivation to make the invention and a reasonable expectation of success. In new fields, such as biotechnology in the 1980s, many approaches that are obvious to try are nonetheless fraught with uncertainty. As a field progresses, however, uncertainty decreases, at least with respect to the likely results of standard experimental designs and approaches. A (non)obviousness inquiry that focuses on reasonable expectation of success should adapt to the changing expectations of those working in a field as further knowledge reduces uncertainty,

[120] *Id.* at 904.

[121] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

[122] A sandwich assay uses two different antibodies that bind to two different sites on an antigen to create a sandwich with antibodies on the outside and antigen in the middle.

[123] *Hybritech Inc.*, 802 F.2d at 1380.

[124] *In re* Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

[125] *Id.* at 493.

although it may be necessary to consult expert testimony to determine where those expectations stood at the time the invention was made.

The Federal Circuit lost sight of this guiding principle in two cases involving the patenting of DNA sequences corresponding to known proteins.[126] Because the Federal Circuit's analysis of these cases is particularly problematic under *KSR*, I review them in some detail. In the early years of the biotechnology industry, isolating a DNA sequence that encodes a known protein was a significant technological challenge, beyond the reasonable expectations of success of a PHOSITA.[127] But over time, this became a routine step using familiar techniques that scientists of ordinary skill would deploy with a reasonable expectation of success.[128] The PTO accordingly began rejecting patent claims covering DNA sequences encoding known proteins,[129] and the applicants appealed the rejections. The Federal Circuit, rather than asking whether the prior art provided a motivation to isolate the gene and the tools to do this work with a reasonable expectation of success, turned instead to the first approximation of chemical obviousness that Judge Rich had rejected as unduly simplistic in *In re Papesch*, beginning and ending the analysis by asking whether the prior art made the structure of the DNA molecule obvious.

In *In re Bell* the applicant claimed DNA and RNA molecules encoding human insulin-like growth factors.[130] The prior art disclosed amino acid sequences for human insulin-like growth factors and general techniques for cloning genes encoding proteins for which a partial amino acid sequence is known. The examiner rejected the claims as prima facie obvious and the Board affirmed, reasoning that "although a protein and its DNA are not structurally similar, they are correspondently

[126] *In re* Bell, 991 F.2d 781 (Fed. Cir. 1993); *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995). For a somewhat different critique that situates these decisions in the Federal Circuit's approach to a variety of doctrinal issues arising in biotechnology cases, see Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 700–02 (2004).

[127] *See, e.g.*, Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1207–08 (Fed. Cir. 1991) ("The district court specifically found that, as of 1983, none of the prior art references 'suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest.' . . . While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success."). Although the Federal Circuit in *Amgen, Inc. v. Chugai Pharmaceutical Co.* followed the lead of the district court and the parties in analyzing the obviousness of the gene by considering the obviousness of the method used to isolate the gene, the court noted in a footnote that the patent claimed products, not processes, and that it was not independently considering whether the products would have been obvious "aside from the alleged obviousness of a method of making them." *Id.* at 1207 n.3.

[128] Kate H. Murashige, *Section 102/103 Issues in Biotechnology Patent Prosecution*, 16 AIPLA Q.J. 294, 297–98 (1989).

[129] *Id.* at 297.

[130] 991 F.2d 781, 782 (Fed. Cir. 1993).

linked via the genetic code," and concluded that there was no evidence "that one skilled in the art, knowing the amino acid sequences of the desired proteins, would not have been able to predictably clone the desired DNA sequences without undue experimentation."[131] The Federal Circuit reversed in an opinion by Judge Lourie. The opinion began by rejecting the proposition "that the 'correspondent link' between a gene and its encoded protein via the genetic code renders the gene obvious when the amino acid sequence is known."[132] The court noted that because of the degeneracy of the genetic code—i.e., because there are multiple DNA sequences that could encode the same amino acid sequence—the amino acid sequence for insulin-like growth factor could be encoded by more than 10^{36} DNA sequences, and nothing in the prior art suggested which of these possibilities was the actual human DNA sequence identified and claimed by Bell. The PTO had therefore failed to establish a prima facie case of obviousness.[133]

This rigid analysis entirely bypasses the perspective of a PHOSITA on the obviousness of a gene corresponding to a known amino acid sequence. With knowledge of even a partial amino acid sequence and standard cloning techniques, a geneticist would have constructed nucleotide probes to find a corresponding cDNA molecule in a cDNA library, with a great expectation of success. The court did not entirely dismiss the relevance of known cloning methods to the obviousness of the gene. Instead, it pointed out that the primary reference cited by the examiner for disclosure of cloning methods in fact "taught away" from the claimed invention because it called for an approach that would not have worked for cloning the gene for insulin-like growth factor.[134] This explicit consideration of cloning methods in the opinion left open the possibility that the court might, in a future case, find a DNA sequence claim obvious as more sophisticated cloning techniques became routine in the art, giving rise to a clearer expectation of success.

This possibility was foreclosed two years later when the Federal Circuit decided *In re Deuel*.[135] Like *In re Bell*, that case involved claims to DNA sequences encoding known proteins. The proteins in the *Deuel* case were heparin-binding growth factors (HBGFs) that stimulate cell division and tissue repair. Deuel isolated and purified HBGFs from bovine uterine tissue, determined a partial amino acid sequence, and used this information to isolate both bovine and human DNA sequences encoding HBGFs. From these DNA sequences, Deuel determined the

[131] *Id.* at 783.

[132] *Id.* at 783–84.

[133] The result might be different, the court observed in dicta, "in a case in which a known amino acid sequence is specified exclusively by unique codons." *Id.* at 784

[134] The probes used by Bell to clone the gene were longer than those recommended in the reference and, contrary to the suggested approach in the reference, included no amino acids that were specified by unique codons. *Id.* at 784.

[135] 51 F.3d 1552 (Fed. Cir. 1995).

corresponding amino acid sequences using the genetic code. The patent application disclosed the native bovine and human HBGF DNA sequences and amino acid sequences that Deuel found, and included both claims that were limited to these particular DNA sequences (claims 5 and 7) and broader claims to all DNA sequences encoding HBGFs with the same amino acid sequences (claims 4 and 6). The examiner found both sets of claims obvious under section 103 based on two references, Bohlen and Maniatis. Bohlen disclosed partial amino acid sequences for human and bovine proteins identified as heparin-binding brain mitogens (HBBMs), useful in repair of neural tissue, that were identical to the sequence of HBGFs.[136] Maniatis disclosed methods of isolating DNA molecules encoding proteins based on knowledge of partial amino acid sequences for the proteins. The Board affirmed the rejection, reasoning that with knowledge of Bohlen's partial amino acid sequence, a PHOSITA would have been motivated to clone the corresponding gene in order to produce larger quantities of a protein with useful mitogenic properties, and the Maniatis reference would have taught how to make the gene with a reasonable expectation of success. On appeal, Deuel argued that the PTO erred in finding prima facie obviousness despite the lack of structurally similar molecules in the prior art, and improperly rejected the claims based on the obviousness of a method of making the molecules. The Federal Circuit agreed, again in an opinion by Judge Lourie, following the same structural analysis deployed in *In re Bell*. As in *In re Bell*, the Federal Circuit in *In re Deuel* quibbled with the Board's analysis of the obviousness of a method of cloning the gene,[137] but ultimately concluded that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs."[138]

Focusing on the proof structure for chemical obviousness that it had affirmed in *In re Dillon*, the Federal Circuit held that the examiner bore the initial burden of establishing a prima facie case of obviousness. The court noted that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound," and that such a relationship "may provide the requisite motivation . . . to obtain

[136] The Federal Circuit notes that both the examiner and the Board "asserted, without explanation, that HBBMs are the same as HBGFs and that the genes encoding these proteins are identical." *Id.* at 1557.

[137] *Id.* at 1556 ("No prior art was cited to support the proposition that it would have been obvious to screen human placental and bovine uterine cDNA libraries for the claimed cDNA clones. Presumably, the examiner was relying on Bohlen's suggestion that HBBMs may be homologous between species, although the examiner did not explain how homology between species suggests homology between tissue types.").

[138] *Id.* at 1559.

new compounds."[139] In this case, "the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious."[140] These molecules would not have been obvious from Bohlen's disclosure "because Bohlen teaches proteins, not the claimed or closely related cDNA molecules" and, echoing *In re Bell*, "[t]he redundancy of the genetic code precluded contemplation of or focus on the specific cDNA molecules of claims 5 and 7."[141]

Had it not been rigidly focused on structural similarity as the sine qua non of chemical obviousness, at this point, the court might have considered whether anything in the prior art *other than* a structurally similar DNA molecule would have motivated a PHOSITA to make the claimed invention with a reasonable expectation of success. Such an analysis would have led the court, as it did the Board, to the conclusion that in this particular field knowledge of a useful protein would motivate a PHOSITA to clone the corresponding gene, just as in the chemical field knowledge of a useful molecule would motivate a PHOSITA to construct homologs, analogs, or isomers. Instead, in an analysis that conflates prima facie obviousness with conception of an invention, the court concluded that the claimed DNA sequences could not be obvious until they were actually isolated and purified:

> [O]ne could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.[142]

The court faulted the Board's theory that a PHOSITA would have been motivated to clone the gene by knowledge of a useful protein and cloning techniques on the ground that it "amounts to speculation and an impermissible hindsight reconstruction of the claimed invention."[143] Ignoring the PTO's determination of a reasonable likelihood of success, the court observed,

> Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare *a* cDNA or made it obvious to prepare *a* cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness.[144]

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[139] *Id.* at 1558.
[140] *Id.*
[141] *Id.*
[142] *Id.*
[143] *Id.*
[144] *Id.* at 1559 (emphasis in original).

Given the Board's conclusion—never explicitly disputed by the Federal Circuit—that the prior art would have given a PHOSITA a reasonable expectation of success in cloning the gene,[145] the observation that obviousness requires something more than "obvious to try" is beside the point. For the same reason, the court misses its mark with the criticism that "[t]he PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods."[146] Such cloning methods are relevant to the obviousness of the compounds because they provide a reasonable expectation of success in making the claimed compounds. This expectation of success, in combination with the motivation to clone the gene arising from knowledge that it encodes a useful protein, puts the claimed sequences within easy reach of a PHOSITA. By analogy to prior cases, such a showing should shift the burden to the applicant to explain why the invention is nonetheless nonobvious. But by putting the burden on the examiner to show that the prior art would allow a PHOSITA to envision the structure of a DNA sequence before holding the sequence even prima facie obvious, the court forecloses this analysis.

Judge Rich's 1963 opinion in *In re Papesch* admonished the PTO to look beyond structure in analyzing the obviousness of a new chemical, directing attention to what the chemical does rather than simply what it looks like.[147] Thirty-two years later, Judge Lourie's 1995 opinion in *In re Deuel* reinstates structural similarity as the keystone of chemical obviousness analysis, preempting further analysis of obviousness for chemicals if the prior art does not permit visualization of their structures.[148]

This analysis seems highly vulnerable to reversal if a similar case were to find its way to the Supreme Court today. It imposes a "rigid and mandatory formula" in lieu of the Supreme Court's preferred "expansive and flexible approach," thereby limiting the (non)obviousness inquiry. It also defies common sense and ignores the problem-solving approach of PHOSITAs in this particular field, with the effect of "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation."[149]

A recent decision of the PTO Board of Appeals suggests that *KSR* has emboldened the PTO to resume rejections of patent claims to DNA sequences encoding known proteins.[150] The claimed invention in that

[145] *Id.* at 1557 ("The Board concluded that 'the Bohlen reference would have suggested to those of ordinary skill in this art that they should make the gene, and the Maniatis reference would have taught a technique for 'making' the gene with a reasonable expectation of success.'").

[146] *Id.* at 1559.

[147] 315 F.2d 381 (C.C.P.A. 1963).

[148] 51 F.3d 1552 (Fed. Cir. 1995).

[149] KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

[150] *Ex parte* Kubin, 83 U.S.P.Q.2d 1410 (Bd. Pat. App. & Interf. 2007).

case was an isolated polynucleotide molecule encoding "NAIL" polypeptides that mediate immune responses.[151] The prior art disclosed an identical polypeptide known as p38, as well as conventional methods of determining both the corresponding amino acid sequence and nucleotide sequence. The Board found that a PHOSITA would have had a reasonable expectation of success in obtaining the NAIL cDNA based on the prior art and therefore affirmed the examiner's rejection on grounds of obviousness. The patent applicant argued that, under *In re Deuel*, it was improper to reject a claim drawn to a specific polynucleotide molecule without any prior art showing or suggesting a structurally similar molecule. The Board initially distinguished *In re Deuel*,[152] and then went on to call into question its continued viability after *KSR* given the Supreme Court's remarks about how an invention that is "obvious to try" may well be obvious:

> The "problem" facing those in the art was to isolate NAIL cDNA, and there were a limited number of methodologies available to do so. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. Thus, isolating NAIL cDNA was "the product not of innovation but of ordinary skill and common sense," leading us to conclude NAIL cDNA is not patentable as it would have been obvious to isolate it.[153]

Although this bold and explicit departure from *In re Deuel* may prompt an appeal to the Federal Circuit, the Board's decision seems well-founded under *KSR*.

Another line of cases from the Federal Circuit on chemical obviousness, beginning with the 1985 opinion of Judge Rich in *In re Durden*,[154] has provoked notable controversy over the relative virtues of flexibility and rigidity. In *In re Durden* the Federal Circuit affirmed rejection of a claim to a method of preparing novel and nonobvious end products using novel and nonobvious starting materials. The examiner had allowed claims to both the starting materials and end products, but rejected the method claims on the ground that the same process had been disclosed in the prior art using similar starting materials. The Board affirmed the rejection by a split vote. On appeal to the Federal Circuit, the applicant fatally conceded "that the claimed process, apart from the fact of employing a novel and unobvious starting material and apart from the fact of producing a new and unobvious product, is obvious,"[155] and did not argue that differences in either the starting materials or the end product "would be expected to affect the reaction in any way which

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[151] *Id.* "NAIL" is an acronym for Natural Killer Cell Activation Inducing Ligand.

[152] *Id.* at 1413.

[153] *Id.* at 1414 (quoting *KSR*).

[154] 763 F.2d 1406 (Fed. Cir. 1985).

[155] *Id.* at 1408.

might render the claimed process unobvious."[156] Instead, the applicant frankly sought a bright-line rule that an otherwise obvious process should be patentable simply because the starting material and end product are novel and nonobvious.[157] Affirming the rejection, the Federal Circuit declined to adopt such a bright-line rule of patentability, insisting upon a flexible, case-by-case approach:

> We are sure that there are those who would like to have us state some clear general rule by which all cases of this nature could be decided. Some judges might be tempted to try it. But the question of obviousness under § 103 arises in such an unpredictable variety of ways and in such different forms that it would be an indiscreet thing to do. Today's rule would likely be regretted in tomorrow's case. Our function is to apply, in each case, § 103 as written to the facts of disputed issues, not to generalize or make rules for other cases which are unforeseeable.[158]

This decision was much criticized by the patent bar[159] and, notwithstanding Judge Rich's insistence that the case should not be read to lay down a clear general rule, the PTO interpreted *In re Durden* broadly to impose a virtual per se rule of obviousness for claims to otherwise conventional processes using new and nonobvious starting materials to make new and nonobvious end products.[160] This result was particularly troubling to the biotechnology industry, which was trying to make a business out of using conventional production techniques to harvest recombinant proteins from genetically engineered host cells. Biotechnology firms sometimes had difficulty obtaining product patent protection for protein products that were otherwise indistinguishable from natural proteins in the prior art. After Congress amended the Patent Act in 1988 to provide a remedy for the sale in the U.S. of a product made abroad through a U.S.-patented process,[161] the rejection of

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[156] *Id.*

[157] *Id.*

[158] *Id.* at 1411.

[159] *See, e.g.*, Karen G. Bender et al., *Patent Decisions of the United States Court of Appeals for the Federal Circuit: The Year 1985 in Review*, 35 AM. U. L. REV. 995, 1005 (1986) (criticizing the Federal Circuit's "disappointing decision in *In re Durden*" which "clearly resulted from the court's refusal to state a general rule of law that a process is automatically patentable by virtue of the patentability of the starting material or end product" notwithstanding that patent law already "gives the owner of a patent on a starting material or an end product the power to enjoin use of the process of using the former and of making the latter").

[160] *See* Harold C. Wegner, *Much Ado About* Durden, 71 J. PAT. & TRADEMARK OFF. SOC'Y 785 (1989); Mark A. Litman, *Obvious Process Rejections Under 35 U.S.C. 103*, 71 J. PAT. & TRADEMARK OFF. SOC'Y 775 (1989).

[161] Omnibus Trade and Competitiveness Act of 1988, Pub. L. No. 100-418, § 9003, 102 Stat. 1107, 1563–64 (1988). The Act added section 271(g) to the patent statute, providing in part:

> Whoever without authority imports into the United States or sells or uses within the United States a product which is made by a process patented in

biotechnology process claims under the authority of *In re Durden* looked like a significant loss to industry.[162]

In two subsequent cases, the Federal Circuit overturned the PTO's rejection of process claims, each time distinguishing *In re Durden* on questionable grounds without overruling it, while reiterating that each case presents unique facts.[163] In Judge Rich's 1990 opinion in *In re Pleuddemann*, the Federal Circuit characterized the appealed claim in *In re Durden* as being for "a method of *making* a compound," while the claims at issue in *In re Pleuddemann* "are for methods of bonding/priming by the use of novel agents invented by appellant for that particular use."[164] Judge Rich spun this distinction out a little further, inviting the inference that methods of using nonobvious products are more likely to be nonobvious and patentable than methods of making such products:

> [T]he compounds and their use are but different aspects of, or ways of looking at, the same invention and consequently that invention is capable of being claimed both as new compounds or as a new method or process of bonding/priming. On the other hand, a process or method of making the compounds is a quite different thing; they may have been made by a process which was new or old, obvious or nonobvious. In this respect, therefore, there is a real difference between a process of making and a process of using and the cases dealing with one involve different problems from the cases dealing with the other.[165]

But this distinction failed to reconcile the cases to the satisfaction of the PTO and the bar.[166]

The issue returned to the Federal Circuit five years later in *In re Ochiai*, on appeal from a rejection of a process of preparing a nonobvious

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> the United States shall be liable as an infringer, if the importation, sale, or use of the product occurs during the term of such process patent . . . .

[162] The poster child for the biotechnology industry's concerns was EPO, a therapeutic protein cloned by Amgen. Although Amgen held a patent on the isolated gene for EPO and recombinant starting materials, because its process claims were rejected under *In re Durden*, Chugai, a Japanese competitor, was able to use Amgen's U.S.-patented materials in Japan and import the protein into the U.S. without any infringement liability to Amgen. Amgen, Inc. v. U.S. Int'l Trade Comm'n, 902 F.2d 1532 (Fed. Cir. 1990); *Hearings on H.R. 587 Before the Subcomm. on Courts and Intellectual Property of the H. Judiciary Comm.*, 104th Cong., 1st Sess. (1995) (statement of Steven M. Odre, Associate General Counsel, Amgen).

[163] *In re* Pleuddemann, 910 F.2d 823 (Fed. Cir. 1990); *In re* Ochiai, 71 F.3d 1565 (Fed. Cir. 1995).

[164] *In re Pleuddemann*, 910 F.2d. at 827 (emphasis in original).

[165] *Id.*

[166] Indeed, the process deemed obvious in *In re Durden*, and distinguished in *In re Pleuddemann*, was not simply a method of *making* nonobvious end products, but also a method of *using* nonobvious starting materials. Moreover, the process at issue in *In re Pleuddemann* had an end product—a bonded composite of polymerizable material and mineral filler, or a primed surface—and could thus be framed as a method of making a product.

cephem compound using a nonobvious organic acid.[167] The PTO allowed claims to both the end product and the starting materials, but rejected the process claims on the ground that they were drawn to a conventional "method of making" and *In re Durden* therefore controlled.[168] While defending the rejection before the Federal Circuit, the PTO Solicitor asserted that there was an irreconcilable conflict in the cases that "makes it very difficult for patent attorneys to give cogent advice to clients or for patent examiners to render consistent decisions on the patentability (under § 103) of processes involving the use of new and unobvious starting materials."[169] The Federal Circuit reversed the rejection in an opinion that seemed to rest on the nonobviousness of the starting materials to defeat the obviousness of the process:

> The process invention Ochiai recites in claim 6 specifically requires use of none other than its new, nonobvious acid as one of the starting materials. One having no knowledge of this acid could hardly find it obvious to make any cephem using this acid as an acylating agent, much less the particular cephem recited in claim 6. In other words, it would not have been obvious to those of ordinary skill in the art to choose the particular acid of claim 6 as an acylating agent for the known amine for the simple reason that the particular acid was unknown but for Ochiai's disclosure in the '429 application.[170]

This analysis might seem to make any process that uses a new and nonobvious product—including the process at issue in *In re Durden*—nonobvious *ipso facto*, but the Federal Circuit denied (without explanation) that the cases were in conflict or that it was applying a per se rule:

> The use of *per se* rules, while undoubtedly less laborious than a searching comparison of the claimed invention—including all its limitations—with the teachings of the prior art, flouts section 103 and the fundamental case law applying it. *Per se* rules that eliminate the need for fact-specific analysis of claims and prior art may be administratively convenient for PTO examiners and the Board. . . . But reliance on *per se* rules of obviousness is legally incorrect and must cease. . . . We once again hold today that our precedents do not establish any *per se* rules of obviousness, just as those precedents themselves expressly declined to create such rules.[171]

By this point the biotechnology industry had taken its case to Congress,[172] and while *In re Ochiai* was pending before the Federal

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[167] 71 F.3d 1565.

[168] *Id.* at 1567–69.

[169] *Id.* at 1569 (internal quotations omitted).

[170] *Id.* at 1569–70.

[171] *Id.* at 1572. *See also In re* Brouwer, 77 F.3d 422 (Fed. Cir. 1995).

[172] Isabelle McAndrews, *Reversing the Burden of* Durden *Through Legislation: HR 3957 and HR 5664*, 72 J. PAT. & TRADEMARK OFF. SOC'Y 1188 (1990).

Circuit, Congress amended section 103 to establish a per se rule of nonobviousness for biotechnological processes.[173] Under the amended statute, a patent applicant may claim a process of using or making new and nonobvious compositions of matter without having the process claims separately examined for nonobviousness, provided the claims to the process and to the composition of matter are in the same application or in applications with the same effective filing date, owned by the same person or subject to an obligation of assignment to the same person, and set to expire on the same date.[174] The legislation is industry-specific and includes a definition of "biotechnological process."[175] Broader proposals for changing the statute for all process claims were opposed by other industries, notably including the chemical industry.

This episode sheds an interesting light on the pressures the Federal Circuit faces in exercising appellate review of (non)obviousness determinations. Notwithstanding its characterization as a question of law, the (non)obviousness of an invention is a highly case-specific, fact-laden inquiry that does not lend itself to generalizations across cases or bright-line rules. Yet the mission of the Federal Circuit is to bring about greater uniformity and predictability in the administration of the patent laws. Both the patent bar and the PTO generally welcome greater clarity in the applicable rules, although in the select universe of cases that come before the Federal Circuit, the patent bar seeks rules that favor patentability while the PTO seeks deference for its rejections. If either side becomes sufficiently unhappy with how the Federal Circuit is performing, they have access to two other institutions that occasionally intervene to change the ground rules: Congress, which intervened to provide the per se rule of patentability for biotechnology processes that the Federal Circuit refused to grant in *In re Durden*, and the Supreme Court, which intervened to relax the Federal Circuit's TSM approach in *KSR*.

The rhetoric of the Federal Circuit in *In re Durden*, *In re Pleuddemann*, and *In re Ochiai* sounds like it could have been written after the Supreme Court's decision in *KSR* by a court that had taken to heart the admonition to avoid the use of "rigid and mandatory formulas" and to follow instead the Supreme Court's own "flexible and expansive" approach. But even when the Federal Circuit affirms its commitment to flexibility and analysis of each case on its facts, as it did repeatedly in *In re Durden*, *In re Pleuddemann*, and *In re Ochiai*, it sometimes seems to have difficulty explaining what differences in the cases are pertinent and

[173] Biotechnological Process Patents Act of 1995, Pub. L. No. 104-41, § 103, 109 Stat. 351 (codified at 35 U.S.C. § 103(b)). The legislative history reflects two principal concerns: providing certainty for patent applicants, and protecting the biotechnology against foreign competition.

[174] The process claims fall with the product claims—that is, if the product claims are held invalid, and the basis for allowing the patent to issue on the process claims was the nonobviousness of the product, the process shall no longer be considered nonobvious solely on the basis of section 103(b).

[175] *Id.*

articulating just what sort of analysis it hopes to see in future cases. Setting aside the rhetoric about the importance of analyzing each case on its own facts, *In re Durden* says next to nothing about what facts make the claimed process in that particular case obvious. *In re Pleuddemann* appeared to highlight as a relevant consideration whether the claimed process was to a "method of making" or a "method of use," with the nonobviousness of the materials more likely to impart patentability to "methods of use." But the court backed away from that distinction in *In re Ochiai* (perhaps because it did not serve to reconcile the cases and made no sense) and made no further effort to distinguish the facts of *In re Durden*. Without providing a clearer account of the basis for its decisions, flexible and expansive decision-making can become peremptory and uninformative and thus fail to offer adequate guidance for resolving future cases.

V. THE FEDERAL CIRCUIT AND PHARMACEUTICAL PATENTS

Perhaps the most commercially significant patents governed by the rules of chemical obviousness are pharmaceutical patents.[176] The Federal Circuit has evaluated many pharmaceutical patents for obviousness in a growing body of caselaw. Many of these cases consider the (non)obviousness question in a different time frame than the cases discussed in the previous Part. The rules for determining the obviousness of chemicals developed primarily in the context of appeals from rejections of patent claims by the PTO, initially to the CCPA and later to the Federal Circuit. These cases were primarily about relatively new inventions that had not yet received patent protection. By contrast, the nonobviousness of drug patents today is more likely to be litigated in a so-called "ANDA infringement" action at a much later stage, after a product has been on the market for some time and is on the verge of facing generic competition.[177]

[176] Empirical studies indicate that this is an area where decision-makers really care about patents when they contemplate spending money on R&D, in contrast to other fields and industries that rate other, non-patent factors as more important. W.M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions & Why U.S. Manufacturing Firms Patent (Or Not) in* WORKING PAPER NO. 7552 (Nat'l Bureau of Econ. Research Working Paper Series, 2000); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECONOMIC ACTIVITY 783 (1987).

[177] "ANDA litigation" is patent infringement litigation that follows the filing of an "Abbreviated New Drug Application" or ANDA, seeking FDA approval to market a generic version of a previously approved product. Complex statutory provisions specify when a firm may submit an ANDA and when the FDA may approve an ANDA for a generic version of a new chemical entity, giving the innovator a period of FDA-administered exclusivity of between 4 and 7 ½ years. *See* 21 U.S.C. § 355(j)(5)(F)(ii). The duration of this exclusivity period turns in part on whether the generic product would infringe patents that have been listed with the FDA, whether the firm submitting an ANDA is challenging the patents, and whether the patent holder

The procedural context for these cases is somewhat idiosyncratic. Patent law and drug regulation converge in ways that promote litigation over the validity of drug patents when a generic competitor seeks to enter the market for a successful drug.[178] The Hatch-Waxman Act of 1984[179] streamlined the regulatory approval process for generic versions of drugs previously approved by the FDA by allowing these products to use an "Abbreviated New Drug Application," known as an ANDA, once applicable patents have expired or been held invalid.[180] Almost inevitably, as successful pharmaceutical products approach the end of their original patent terms, their sponsors obtain additional patents on related inventions to forestall generic entry. If a generic competitor seeks regulatory approval prior to the expiration of any of these patents, it must certify to the FDA that the patent is either invalid or will not be infringed by its generic version of the product. At that point, the patent owner has an opportunity to sue for infringement and to litigate the patent issues prior to FDA approval of the generic product. To encourage challenges to invalid patents, the Hatch-Waxman Act gives the first successful patent challenger a six-month period of lucrative "generic exclusivity" before it will approve another generic version of the same product.[181]

These provisions have provoked extensive patent litigation as research pharmaceutical firms and generic competitors have explored their strategic implications, giving the Federal Circuit many opportunities to address the validity of drug patents. Because hundreds of millions or even billions of dollars turn on how these disputes are resolved, both plaintiffs and defendants[182] may find it worthwhile to press claims and arguments that have only a slim chance of carrying the day, and appeals are typical. At this stage, the patents have issued and enjoy a presumption of validity, and considerable information is available, to both the patent holder and the challenger, about the product and its properties from laboratory testing, clinical trials, and clinical experience.

The Federal Circuit scrutinizes these cases with great care and shows considerable awareness of their unusual regulatory and strategic context. In these cases the Federal Circuit has attempted to integrate the rules for

responds by filing a patent infringement action. For a summary and analysis of the applicable law, see Rebecca S. Eisenberg, *The Role of FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007).

[178] *Id.*

[179] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28, and 35) (commonly known as the "Hatch-Waxman Act").

[180] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j) (2000).

[181] 21 U.S.C. § 355(j)(5)(B)(iv).

[182] Of course patent holders typically stand to earn more money from sales of a product for which they face no competition than challengers stand to earn from entering the market as generic competitors, and patent holder can therefore be expected to spend much more on ANDA litigation than challengers.

chemical obviousness within its broader (non)obviousness jurisprudence, resulting in some doctrinal confusion. Nonetheless, overall the (non)obviousness decisions of the Federal Circuit in pharmaceutical cases reveal considerable flexibility and case-by-case analysis. In contrast to cases decided on appeal from PTO rejections, in which inability to meet the burden of producing unavailable evidence may be decisive, infringement cases typically arrive at the Federal Circuit after a full record has been developed in litigation, and analysis of nonobviousness is more likely to reach the merits. Although there appear to be some disagreements among the judges of the Federal Circuit and some decisions have provoked sharp dissents, most panels do not display the pro-patent bias that is sometimes attributed to that court.

From a formal perspective, there are reasons to expect the Federal Circuit to show greater deference to obviousness determinations of the PTO than to obviousness determinations of the district courts. The Patent Act accords a presumption of validity to issued patents, and challengers bear a burden of proof by clear and convincing evidence to establish the obviousness of an invention that is covered by an issued patent.[183] Moreover, the Supreme Court admonished the Federal Circuit in *Dickinson v. Zurko* that under the Administrative Procedure Act factual findings of the PTO are entitled to greater deference than factual findings of courts.[184] One might therefore expect the Federal Circuit to display greater deference to findings of obviousness on appeals from decisions of the PTO, before any patent has issued, while scrutinizing more skeptically obviousness determinations by district courts that overturn the validity of presumptively valid issued patents.[185]

In practice, however, the Federal Circuit seems if anything more deferential toward the (non)obviousness determinations of trial courts. One reason for this may be that most of the Federal Circuit's decisions about (non)obviousness have turned on rules about proof rather than on application of an actual substantive standard to determine the (non)obviousness of an invention. In appeals from decisions of the PTO, the evidentiary record is sparse, consisting primarily of documentary prior art, and the burden of proof is therefore difficult to sustain. In high

[183] 35 U.S.C. § 282 (2000).

[184] 527 U.S. 150, 164 (1999).

[185] On the other hand, if one takes seriously judicial statements that the ultimate conclusion as to (non)obviousness is a question of law, subject to de novo review on appeal, one might expect appellate review to be substantially the same whether the appeal is from the PTO or a court. In *Graham*, the Supreme Court noted that "the primary responsibility for sifting out unpatentable material lies in the Patent Office" and complained that "[w]e have observed a notorious difference between the standards applied by the Patent Office and by the courts," implying that the (non)obviousness standard should be the same in both contexts. 383 U.S. 1, 18 (1966). The Court called upon the PTO to "strictly adhere to the 1952 Act as interpreted here" in order to "bring about a closer concurrence between administrative and judicial precedent." 383 U.S. at 18–19.

stakes infringement litigation, by contrast, the parties have ample opportunity and motivation to develop a full record, including expert testimony and post-invention evidence of differences between the invention and the prior art. In the face of such a record, the Federal Circuit has relatively few moves available to overturn district court decisions.

The Federal Circuit typically deploys the same analytical tools whether it is reviewing (non)obviousness determinations of the PTO or of the district courts. The Federal Circuit has folded its approach to chemical obviousness, originally developed in reviewing decisions of the PTO, into its articulation of the proper approach for district courts in reviewing the validity of issued patents. Some aspects of the chemical obviousness approach seem off point in this framework, resulting in doctrinal confusion. For example, in the context of patent prosecution, the burden is initially on the examiner to establish a prima facie case of obviousness, typically through a showing of structural similarity to a useful molecule in the prior art. Once this showing is made, the burden then shifts to the applicant to rebut the prima facie case, typically by showing that the claimed invention has unexpected properties not possessed by the structurally similar prior art. This shifting of the burden seems appropriate at the prosecution stage, when there is no presumption of validity and little information is available about the product. The examiner is in no position to know the properties of the new chemical, but should be able to search the prior art for structurally similar molecules. If this search reveals prior art that makes the invention prima facie obvious, the applicant is in a better position than the examiner to offer further evidence about the properties of the invention, since only the applicant has had the opportunity to observe the new chemical and to test its properties. It makes considerably less sense, however, to place the same burden on the patent owner at the later stage of patent enforcement. At this point, the patent enjoys a presumption of validity, calling into question the logic of requiring the patentee to make any showing of validity. Moreover, the challenger is likely to be a commercial competitor who has knowledge of the properties of the invention and opportunity to compare it to the prior art. In the infringement context, the burden of proof of obviousness by clear and convincing evidence formally remains on the challenger at all times, yet the Federal Circuit still refers to the showing of structural similarity, somewhat confusingly, as a "prima facie case" of obviousness.[186]

In some cases the court has analyzed the (non)obviousness of pharmaceutical products without resort to the special rules for evaluating the patentability of chemicals. For example, a number of cases consider the obviousness of pharmaceutical compositions that combine well-known ingredients in a single formulation to treat symptoms that

[186] *E.g.*, Pfizer, Inc., v. Apotex, Inc., 480 F.3d, 1348 1359–60 (Fed. Cir. 2007); Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369 (Fed. Cir. 2006).

typically occur together. In *Richardson-Vicks Inc. v. Upjohn Co.*, the Federal Circuit affirmed a trial court judgment of invalidity for a claimed formulation of ibuprofen and pseudoephedrine in a "combinatory immixture" for relief of cough, cold, and flu.[187] The court concluded that the invention would have been obvious in light of prior art that included a combination of acetaminophen and pseudoephedrine, a combination of aspirin and pseudoephedrine, and the practice of doctors to prescribe ibuprofen in combination with pseudoephedrine, although not in a "combinatory immixture."[188] The court looked to features of the over-the-counter (OTC) drug marketplace to explain the obviousness of the invention. Noting that at the time of the invention it had been widely reported that the FDA would soon approve ibuprofen for OTC sales, the court surmised that this regulatory shift would motivate the OTC industry to substitute ibuprofen for acetaminophen or aspirin to create a combination product with superior analgesic properties and fewer side effects.[189] Similarly, in *McNeil-PPC v. L. Perrigo Co.*, the Federal Circuit affirmed a trial court judgment of invalidity for a claimed method of treating intestinal disorders characterized by both diarrhea and flatulence by administering a combined pharmaceutical composition that includes an effective antidiarrheal compound with the antiflatulent compound simethicone.[190] The prior art disclosed each of the components and information about their dosing, products that combined other antidiarrheals with simethicone, and more than twenty publications that noted the concurrence of diarrhea and flatulence.[191] The court quoted at length from the district court's angry opinion accusing the patent holder of filing and litigating patents on trivial advances to extend its period of exclusivity for years beyond the expiration of a basic patent on its best-selling product Immodium® A-D.[192] In each of these cases the court considered proffered evidence of unexpected or synergistic results for the product and found it unpersuasive.

By contrast, the Federal Circuit faulted the trial court for refusing to consider evidence of surprising results for a combination product in *Knoll Pharmaceutical Co., Inc. v. Teva Pharmaceuticals USA, Inc.*[193] The Federal Circuit reversed a grant of summary judgment of invalidity for a patent that claimed methods and compositions for treating pain with a combination of hydrocodone and ibuprofen.[194] Although agreeing with the trial court that the prior art suggested the combination, the Federal

[187] 122 F.3d 1476, 1481 (Fed. Cir. 1997).
[188] *Id.* at 1483–84.
[189] *Id.* at 1484.
[190] 337 F.3d 1362 (Fed. Cir. 2003).
[191] *Id.* at 1369–70.
[192] *Id.* at 1367–68.
[193] 367 F.3d 1381 (Fed. Cir. 2004).
[194] *Id.* at 1382–83.

Circuit found no prior art teaching or suggestion that the combination would have an enhanced effect.[195] The trial court had refused to consider the patent holder's proffered evidence of surprising results on the theory that these benefits were not discovered until after the patent had issued.[196] The Federal Circuit held that it was error to exclude this post-invention evidence in support of the patent:

> Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity. There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.[197]

Although the Federal Circuit has been fairly consistent in holding that evidence of surprising properties should be considered in evaluating an invention for (non)obviousness, it often categorizes such evidence as "secondary evidence" of nonobviousness, putting it in the same category as evidence of commercial success, failure of others, and long-felt but unsolved need.[198] Evidence of surprising or unexpected properties is unlike these other sources of "market" evidence that indicate obviousness only through a chain of inferences. It is primary, technological evidence going directly to the statutory inquiry as to "the differences between the subject matter sought to be patented and the prior art."[199] As Judge Rich explained in *In re Papesch*, "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."[200] In other words, evidence of the properties of a chemical is directly relevant to show what the claimed invention is. The characterization of this evidence as "secondary" seems fundamentally confused, and it could make a difference if it leads to a discounting of the relevance of surprising properties in the overall conclusion as to obviousness.

The coding of surprising properties evidence as "secondary" may have led the Federal Circuit to discount its relevance in its recent decision in *Pfizer, Inc. v. Apotex, Inc.*[201] The patent at issue in that case

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[195] *Id.* at 1384–85.

[196] *Id.*

[197] *Id.* at 1385.

[198] *E.g.*, Eli Lilly & Co. v. Zenith Goldline Pharm., Inc, 471 F.3d 1369, 1380 (Fed. Cir. 2006); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1369–72 (Fed. Cir. 2007).

[199] 35 U.S.C. § 103(a) (2000).

[200] 315 F.2d 381, 391 (C.C.P.A 1963).

[201] 480 F.3d 1348 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 110 (2007).

claimed the besylate salt of amlodipine, the active ingredient in the blood pressure medication Norvasc®.[202] The prior art included besylate salts of other compounds, as well as Pfizer's own prior patent covering all pharmaceutically acceptable acid addition salts of amlodipine, but no reference explicitly mentioned the besylate salt of amlodipine.[203] After beginning clinical trials with its originally preferred maleate salt Pfizer encountered problems with instability and stickiness, and made and tested other amlodipine salts to find one that was easier to handle.[204] Finding that the besylate salt was the best, Pfizer changed to the besylate salt in its clinical trials, and patented it.[205] Three district courts upheld the validity of the patent, but a Federal Circuit panel reversed. The panel held that on the evidence presented a reasonable fact-finder could only conclude that "Apotex has shown by clear and convincing evidence that the skilled artisan would . . . have been . . . motivated to combine the prior art to produce the besylate salt of amlodipine," and that "the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine."[206]

The panel then turned to a consideration of "secondary considerations," and under this heading addressed the district court's conclusion that the besylate salt was nonobvious because it was more stable and less sticky than the maleate salt of amlodipine.[207] The court held that the record failed to show that these properties were unexpected, noting that both the maleate salt and the besylate salt were therapeutically effective, as were the other acid addition salts, and that the selection of the besylate salt for its superior ease of handling and projected shelf-life "proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art."[208] The court went on to offer as an alternative ground for its decision that mere "secondary" evidence of superior properties was not sufficient to overcome the strong prima facie case of obviousness:

> Alternatively, we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. Here, the record establishes such a strong case of obviousness that Pfizer's alleged unexpectedly superior results are ultimately insufficient.[209]

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[202] *Id.* at 1352.
[203] *Id.* at 1361–62.
[204] *Id.* at 1353–54.
[205] *Id.* at 1354–55.
[206] *Id.* at 1361.
[207] *Id.* at 1369–70.
[208] *Id.* at 1371.
[209] *Id.* at 1372 (citation omitted).

Since this was an alternative ground of decision, it is difficult to say whether the coding of the superior properties of amlodipine besylate as "secondary evidence" made a difference. The fact that the court went to the trouble of laying out multiple pathways to its invalidity conclusion suggests that it felt highly motivated to find the patent invalid. Perhaps the court was influenced by the fact, noted in its opinion, that Pfizer's original patent covering all pharmaceutically acceptable salts of amlodipine, including amlodipine besylate, had by this point expired at the end of its extension term.[210] The subsequent patent on amlodipine besylate may have seemed like improper patent "evergreening" of a product that had already enjoyed a healthy term of patent protection and belonged in the public domain.[211]

Another way of understanding the decision in *Pfizer, Inc. v. Apotex, Inc.* is that the superior properties of the besylate salt were not surprising enough to make the choice of one salt over another nonobvious:

> [T]he record is devoid of *any* evidence of what the skilled artisan would have expected. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. . . . Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. . . . The fact that amlodipine besylate was the best of the seven acid addition salts *actually tested* proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art.[212]

The Federal Circuit has been more generous in finding unexpected properties when the claimed invention is a new drug with a distinct safety and efficacy profile relative to the prior art, even if the prior art discloses

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[210] *Id.* at 1353 n.2. Drug developers are entitled to extend the term of protection for one patent per product in order to make up for some of the time lost seeking regulatory approval. 35 U.S.C. § 156 (2000). In this case, the patent selected for extension was the broader patent covering all pharmaceutically acceptable salts, not the narrower patent in suit that covered only the besylate salt. Paul Johnson, in thoughtful comments on an earlier draft, suggests that the court may have been motivated to invalidate the patent on the eve of its expiration so that Apotex, as the patent challenger, could claim the benefit of a 180-day period of "generic exclusivity" before other ANDAs could be approved. See *supra* note 181 and accompanying text.

[211] *See also In re* Merck & Co., 800 F.2d 1091, 1096–98 (Fed. Cir. 1986) (holding invalid for obviousness a patent with a priority date twenty-seven years prior to date of opinion on a method of treating depression by administering amitriptyline over prior art disclosing amtriptyline, structurally similar imipramine, use of imipramine to treat depression, and explicit suggestion to try amtriptyline as a treatment for depression) The Federal Circuit has used a variety of doctrinal tools to invalidate "evergreening" patents. *See* Eisenberg, *supra* note 177.

[212] 480 F.3d at 1371 (emphases in original).

structurally similar molecules. One way that the Federal Circuit has sometimes upheld patentability for such products is by asking whether the most structurally similar prior art would have been selected as a "lead compound" in developing a new drug. For example, in *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.,* the Federal Circuit affirmed a district court judgment as a matter of law upholding the validity of a patent claiming famotidine, sold under the brand name Pepcid®.[213] Famotidine was a member of a class of drugs called H[2] antagonists, and the prior art disclosed thousands of H[2] antagonists, including a structurally similar molecule that was set forth as example 44 in a prior patent to Yamanouchi.[214] In affirming the district court, the Federal Circuit recited a series of steps that Danbury failed to show a PHOSITA would have been motivated to take in order to arrive at famotidine, beginning with the selection of example 44 as a lead compound, followed by further combinations and substitutions.[215] The court remarked upon the markedly superior properties of famotidine over the prior art, although ultimately concluding that it was unnecessary to consider "the strong objective evidence of non-obviousness" because Danbury failed even to make a prima facie showing of obviousness.[216]

The Federal Circuit cited Yamanouchi with approval in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*,[217] in which it affirmed a district court judgment that the challenger had failed to establish the invalidity of a patent on the anti-schizophrenia drug olanzapine. Olanzapine was a novel member of a family of compounds that included clozapine, an anti-schizophrenia drug that had been taken off the market years earlier because of its bad side effects. The prior art disclosed a number of structurally similar compounds including Compound 222, an adjacent homolog of olanzapine. The district court found that the prior art would not have motivated a PHOSITA to use Compound 222 as a lead compound because it contained a hydrogen atom in the place of a flourine atom that was thought essential to the antipsychotic properties of clozapine and other antipsychotics. The challengers argued on appeal that the district court erred by requiring them to "establish a teaching or incentive to treat the closest prior art (i.e., Compound '222) as a 'lead compound'" rather than permitting them to establish prima facie obviousness based on disclosure in the prior art of an adjacent homolog.[218] In affirming the district court's rejection of the obviousness challenge, the Federal Circuit analyzed the facts in a way that blended consideration of the prima facie case and rebuttal evidence. They reiterated the district court's finding that defendants had failed to show

[213] 231 F.3d 1339, 1341–42 (Fed. Cir. 2000).
[214] *Id.* at 1343–44.
[215] *Id.* at 1344–45.
[216] *Id.* at 1345.
[217] 471 F.3d 1369 (Fed. Cir. 2006).
[218] *Id.* at 1377.

that a PHOSITA would have selected Compound 222 as a lead compound, without disapproving of this threshold requirement, in considering whether the prior art would have motivated or taught away from the structural modifications that were necessary to make olanzapine. They also noted that Lilly had proved "extensive secondary considerations to rebut obviousness," including unexpected results.[219]

The Federal Circuit followed a similar analysis in its post-*KSR* opinion in *Takeda Chemical Industries v. Alphapharm Pty., Ltd.*, affirming a district court judgment that the challenger had failed to establish the obviousness of a patent on pioglitazone, the active ingredient in the successful Type 2 diabetes drug ACTOS®.[220] The prior art included prior patents to Takeda. One of these patents, the '200 patent, disclosed a genus of thiazolidine (TZD) compounds and specifically identified fifty-four compounds, including compound b. Compound b was structurally similar to pioglitazone, and the prosecution history of the '200 patent included data showing that compound b had antidiabetic properties. Another prior art patent of Takeda, the '779 patent, specifically claimed compound b, and the prosecution history identified it as especially important. But another prior art reference, Sodha II, disclosed data from studies of 101 TZD compounds and singled out compound b as causing "considerable increases in body weight and brown fat weight."[221] Sodha II identified three compounds, not including compound b, as being the most favorable in terms of toxicity and activitiy. The district court concluded that the prior art as a whole would not have led a PHOSITA to select compound b as a lead compound, and therefore concluded that Alphapharm had failed to show prima facie obviousness by clear and convincing evidence. In affirming, the Federal Circuit panel further noted that the district court "found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds," crediting expert testimony that these steps were not routine at the time.[222] The Federal Circuit recited, evidently with approval, the district court's conclusions that a PHOSITA would not have expected these modifications to ameliorate the unwanted side effects of compound b.[223] Moreover, Takeda's showing that pioglitazone lacked these side effects was sufficient to rebut any showing of prima facie obviousness.[224]

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[219] *Id.* at 1380.

[220] 492 F.3d 1350, 1352 (Fed. Cir. 2007).

[221] *Id.* at 1358.

[222] *Id.* at 1360.

[223] *Id.* at 1362–63. This is arguably inconsistent with the Supreme Court's statement in *KSR* that the focus of (non)obviousness analysis should not be limited to the problem that the inventor was trying to solve, but should consider more broadly whether the claimed invention would have been an obvious solution to any other problem at the time that might have motivated its creation. 127 S. Ct. at 1742.

[224] *Id.* at 1362.

The focus on whether a PHOSITA would have selected the closest prior art molecule as a "lead compound" is an interesting move that makes it easier to establish nonobviousness for new chemical entities that have not previously been developed as drugs. New drugs are often structurally similar to prior art compounds that, for one reason or another, have not been selected for development through clinical trials. A robust nonobviousness standard would present a risk that these undeveloped products would stand as an obstacle not only to their own future development, but also to the future development of any structurally similar compounds.[225] The lead compound approach makes it easier for a firm that later revisits these previously unpromising products and modifies them to serve new purposes to obtain patent protection on new modifications, thereby preserving incentives to undertake the further investment in clinical trials necessary to bring these products to market. At the same time, it excludes from patent protection similar modifications of more salient products, such as already successful drugs, because a PHOSITA would clearly be motivated to use a successful drug as a lead compound in future research. The practical effect is to make it more difficult to obtain evergreening patents on new versions of successful products, while still preserving opportunities to patent modified versions of less salient products that are nonetheless disclosed in the prior art. This approach shows flexibility in adapting (non)obviousness doctrine to the context of biopharmaceutical research and development.

If the Federal Circuit has been especially generous in evaluating the (non)obviousness of new therapeutic agents, it has been especially skeptical of claims for new formulations of old products, particularly when the results are unsurprising. For example, in *Alza Corp. v. Mylan Laboratories, Inc.*,[226] the court began its analysis of a patent on a once-daily, controlled-release formulation of the anti-incontinence drug oxybutynin with the observation that "[o]nce-a-day dosing provides the usual benefits of convenience, steady-dosing, and in addition, possibly reduced absorption of a metabolite that leads to side-effects."[227] Alza argued that an extended release formulation for oxybutynin would have been nonobvious at the time it was made because a PHOSITA would not have believed that oxybutynin could be absorbed in the colon and would therefore have lacked motivation to make such a formulation. But in the face of expert testimony to the contrary, the Federal Circuit deferred to the district court's finding of an implicit motivation and expectation of success for the claimed formulation.[228] Similarly, in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, the Federal Circuit held invalid a patent on a

[225] *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEXAS L. REV. (forthcoming 2008).

[226] 464 F.3d 1286 (Fed. Cir. 2006).

[227] *Id.* at 1288.

[228] *Id.* at 1293.

method for treating and preventing osteoporosis by administering biphosphonate compounds on a less than daily basis.[229] The patent holder argued that the prior art revealed gastrointestinal side effects for the product, including dose-related irritation to the esophagus, that made the success of such a regimen unexpected, and the district court agreed, but the Federal Circuit reversed, citing a prior art reference that proposed weekly dosing to improve patient compliance.[230]

An important area in which the decisions of the Federal Circuit have been mixed concerns the patentability of claims to a particular enantiomer of a drug—i.e. a particular spatial arrangement of the constituent atomic elements of the drug molecule around a chiral center—when the prior art discloses a mixture (called a racemic mixture or racemate) of two possible enantiomers.[231] Often either the therapeutic benefits or side effects of a drug having one chiral center are attributable to only one enantiomer in the racemate, and resolving the racemate (i.e., purifying out the enantiomer with the desired effects) may thus provide a superior product. A series of old decisions of the CCPA held that the isolation of a single stereoisomer from a racemic mixture was prima facie obvious, but that this prima facie showing of obviousness could be rebutted by evidence of unexpected results.[232] The Federal Circuit has revisited these rules repeatedly in recent years.

Siding with the patent holder, the Federal Circuit upheld a district court grant of a preliminary injunction against infringement of a patent claiming a particular enantiomer of a particular salt of a compound called MATTPCA (the active ingredient in Plavix®) in *Sanofi-Synthelabo v. Apotex, Inc.*[233] The panel, in an opinion authored by Judge Lourie, noted "the deferential standard we apply in reviewing grants or denials of preliminary injunctions" and the presumption of validity in concluding

[229] 395 F.3d 1364, 1372 (Fed. Cir. 2005).

[230] *Id.* at 1373–75.

[231] It has long been known that for many chemicals, including drugs, the same constituent atomic elements may form different spatial arrangements called isomers. Generally speaking, stereoisomers are isomers whose three-dimensional shape is dictated by the arrangement of covalent bonds to an atom known as a chiral center. Some stereoisomers, called enantiomers, are mirror images of each other. A mixture of equal amounts of the two enantiomers of a molecule with a single chiral center is called a racemic mixture or racemate. Some compounds have two or more chiral centers, resulting in multiple possible spatial arrangements known as diastereomers. The Federal Circuit considered the patentability of a single diastereomer over a prior art disclosure of a mixture of diastereomers in *Aventis Pharma Deutschland v. Lupin*, discussed *infra*, footnotes 242–46.

[232] *See, e.g.*, *In re* Adamson, 275 F.2d 952, 954–55 (C.C.P.A. 1960) (holding isolated stereoisomer obvious over racemic mixture of stereoisomers, given insufficient showing of unexpected result); *cf. In re* May, 574 F.2d 1082, 1090–94 (C.C.P.A. 1978) (holding isolated stereoisomer nonobviousness over racemic mix, despite prima facie obviousness, because of unexpected property of being nonaddictive).

[233] 470 F.3d 1368, 1372 (Fed. Cir. 2006).

that the district court did not clearly err in finding that the challenger failed to establish a likelihood of proving invalidity at trial.[234] The prior art included an earlier patent claiming MATTPCA, but without explicitly describing its stereoisomers or salts. The district court concluded that the prior art would not motivate a PHOSITA to pursue the claimed enantiomer of the bisulfate salt of MATTPCA, noting "the unpredictability of the pharmaceutical properties of the enantiomers and the potential for enantiomers to racemize in the body, . . . [and] the extensive time and money Sanofi spent developing the racemate before redirecting its efforts toward the enantiomer, and the unpredictability of salt formation."[235] The district court also concluded that any evidence of prima facie obviousness was rebutted by evidence of the unexpected properties of high pharmacological activity and low toxicity.

The Federal Circuit distinguished the 1960 case of *In re Adamson*.[236] In that case the CCPA had affirmed rejection of claims to a particular enantiomer of a compound and its acid addition salts as obvious in view of disclosure in the prior art of (1) compounds of the same formula without mention of racemic mixtures or enantiomers and (2) methods of separating racemic mixtures into their enantiomers.[237] The panel noted two grounds for distinction: first, while it was undisputed in *Adamson* that the prior art disclosed racemic mixtures of the enantiomers and their acid addition salts, in the instant case the prior art "does not disclose the bisulfate salt of the d-enantiomer of MATTPCA"; and second, in the instant case "the district court made factual findings that resolving the racemate was not mere routine experimentation and that it was unexpected that the desirable activity of clopidogrel would be found only in the d-enantiomer."[238] These findings, which the panel did not find clearly erroneous, were sufficient to distinguish *Adamson* and to affirm the preliminary injunction.

In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, another decision authored by Judge Lourie, a different Federal Circuit panel again focused on the difficulty of resolving the racemate into distinct enantiomers, as well as on failure of the prior art to predict which enantiomer would prove more valuable, in affirming the district court's finding that a patent claiming a substantially pure enantiomer had not been proven invalid.[239] The patent at issue in that case covered a substantially pure (+)-enantiomer of the drug citalopram, a selective serotonin reuptake inhibitor, and non-toxic acid addition salts thereof. The plaintiff also owned an expired patent on the racemic form of citalopram. The challengers argued that (+)-citalopram was obvious in

[234] *Id.* at 1375.
[235] *Id.* at 1378–79.
[236] 275 F.2d 952 (C.C.P.A. 1960).
[237] *Id.* at 954–55.
[238] *Sanofi-Synthelabo*, 470 F.3d at 1380.
[239] 501 F.3d 1263, 1265 (Fed. Cir. 2007).

light of disclosure in the prior art of racemic citalopram and techniques to separate enantiomers from a racemic mix. A prior art reference (Smith) predicted that one citalopram enantiomer in the racemic mix would be more potent than the other, but incorrectly predicted that the (–)-enantiomer would be more potent rather than the (+)-enantiomer claimed in the patent at issue.[240] The district court found that the Smith reference did not enable a PHOSITA to obtain substantially pure (+)-citalopram, that many chemists had failed in their efforts to resolve racemic citalopram, and that a PHOSITA attempting to resolve racemic citalopram would have had no reasonable expectation of success.[241] The district court further credited the plaintiff's rebuttal evidence demonstrating the difficulty of separating the enantiomers and the unexpected properties of (+)-citalopram, which had twice the potency of the racemic mix.[242] The Federal Circuit affirmed, again concluding that the district court's findings were not clearly erroneous. Surprisingly, the Federal Circuit opinion in *Forest Laboratories* did not even cite the decision of the Supreme Court in *KSR*, which had come down more than four months earlier.

A week later a different Federal Circuit panel came out the other way, following careful analysis of *KSR*, in *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*[243] The drug at issue in that case, the ACE-inhibitor ramipril, had five chiral centers that could each take either of two special orientations of the surrounding atoms (R or S), for a total of 2^5 (i.e. 32) possible stereoisomers. The district court had concluded after a bench trial that the challenger failed to show by clear and convincing evidence that the claimed invention, 5(S) ramipril in a formulation "substantially free of other isomers," would have been obvious at the time it was made in light of the prior art. The closest prior art disclosed a mixture of two stereoisomers of ramipril, the 5(S) form and the SSSSR form, while the claimed invention was substantially pure 5(S) ramipril. The district court had noted that this was a close case and that the outcome might have been different if the burden of proof had been by a preponderance of the evidence rather than by clear and convincing evidence. Deciding the case prior to *KSR*, the district court found insufficient evidence of motivation to purify 5(S) ramipril.[244] The Federal Circuit panel reversed, concluding that "[r]equiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is the active ingredient is precisely the sort of rigid application of the TSM test that was criticized in *KSR*."[245] In the chemical arts, the court continued, structural similarity to a prior art compound has long been sufficient to provide an implicit

[240] *Id.* at 1268.
[241] *Id.* at 1268–69.
[242] *Id.* at 1269.
[243] 499 F.3d 1293, 1303 (Fed. Cir. 2007).
[244] *Id.* at 1299.
[245] *Id.* at 1301.

motivation to make the claimed subject matter in the expectation that it will have similar properties to the prior art. "The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art . . . . isolation of interesting compounds is a mainstay of the chemist's art."[246] Given that the prior art taught that the stereoisomers of ramipril could be separated by conventional methods, the purified 5(S) stereoisomer was prima facie obvious. The panel was unimpressed by rebuttal evidence that 5(S) ramipril was eighteen times as potent as the next most potent stereoisomer, the RRSSS form. The proper comparison was not to the next most potent stereoisomer, but to the racemic mix of the 5(S) and SSSSR stereoisomers that constituted the closest prior art. Moreover, "the potency of pure 5(S) ramipril is precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers."[247] The court concluded that the patent holder had failed to rebut the case of prima facie obviousness by showing unexpected results.

These cases are not necessarily inconsistent with each other. Each opinion reviews a different evidentiary record to determine whether the prior art would have motivated a PHOSITA to isolate the claimed isomer with a reasonable expectation of success, whether the prior art taught the PHOSITA how to do so, and whether the isolated molecule exhibits surprising properties. The facts of each case are unique. Nonetheless, it is difficult to find a basis for distinguishing the cases that would provide meaningful guidance in future cases. Given that each case involved a claim to a stereoisomer of a successful drug, it is difficult to argue that the prior art did not provide motivation to resolve the racemic mixture. Moreover, it is difficult to distinguish the cases on the basis of differences in properties for the claimed stereoisomer relative to the prior art racemic mixture. Perhaps *Forest Laboratories* and *Aventis Pharma Deutschland* may be distinguished on the basis of the degree of difficulty involved in separating the prior art mixture into purified stereoisomers. But the focus on the method of arriving at the purified stereoisomer, reminiscent of the analysis of the (non)obviousness of DNA sequence claims prior to the decisions in *In re Bell* and *In re Deuel*,[248] is at least in tension with the admonition in those and other cases that the proper focus in evaluating a product for (non)obviousness should be on the product itself rather than on the method of making it.[249]

[246] *Id.* at 1301–02.

[247] *Id.* at 1302.

[248] See *supra* notes 8, 19 and accompanying text.

[249] Paradoxically, it was Judge Lourie who both adamantly discredited the approach of focusing on cloning methods in evaluating the (non)obviousness of DNA sequences in *In re Bell* and *In re Deuel*, and who emphasized the difficulty of resolving the racemic mixture into its constituent enantiomers in *Forest Laboratories v. Ivax*.

The decision in *Aventis Pharma Deutschland* provides some evidence that the Federal Circuit is taking the Supreme Court's decision in *KSR* to heart in evaluating pharmaceutical patents for obviousness. But even prior to that decision, the Federal Circuit was deploying its nonobviousness toolkit with special care and flexibility in pharmaceutical patent cases. In this context, especially when it has the benefit of a full record in the trial court, the Federal Circuit has shown a willingness to look at all the evidence, including post-invention evidence of the properties of the invention, to distinguish nonobvious inventions from the routine results of ordinary skill and common sense. It has not confined its attention to the explicit teachings of documentary references, but has shown a keen awareness of how the workings of the pharmaceutical marketplace structure incentives to modify existing products. It has, in other words, been doing all along what the Supreme Court criticized it for failing to do in *KSR*.

Comparing the decisions of the Federal Circuit on the (non)obviousness of pharmaceutical patents with its broader (non)obviousness jurisprudence, it sometimes seems that the Federal Circuit is more inclined to find the pharmaceutical patents invalid. Perhaps this is because the pharmaceutical industry is obtaining and seeking to enforce many invalid patents. Lucrative exclusivity in the market for a successful drug may make it seem worthwhile to pursue questionable patents as far as the courts will permit. In addition to the possibility of getting a judicial remedy, the filing of an infringement action against a generic challenger may forestall FDA approval of the generic product for a thirty-month period, even if the patent is ultimately held invalid. But pharmaceutical profits also motivate generic challengers to show invalidity, especially given the provision in the Hatch-Waxman Act for a profitable six month head-start for the first successful generic challenger.

By the time these cases come before the Federal Circuit, there is a full record available to help the court separate the wheat from the chaff, enabling it to get beyond the limitations in the evidentiary record that often make appeals from decisions of the PTO turn on allocation of the burden of proof rather than on the merits. Perhaps the Federal Circuit is more willing to find patents invalid on the basis of a full record, while on the lighter record available in appeals from PTO decisions it is more inclined to give patent applicants the benefit of a doubt.

The Federal Circuit showed little deference to the PTO's decision to reject for obviousness in *In re Sullivan*,[250] just a few months after *KSR*. The invention at issue in that case was an antivenom composition for treating snake bites. The claimed composition used only a fragment, called a Fab fragment, of a whole antibody derived from the serum of an animal exposed to the venom. The prior art disclosed whole antibodies against

[250] 498 F.3d 1345, 1347 (Fed. Cir. 2007).

snake venom, a method for producing Fab antibodies in place of whole antibodies, and the use of Fab antibodies to detect snake toxins. The applicant sought to distinguish this prior art through amended claim language specifying an intended use for treating snake bites and reciting that the composition neutralizes the lethality of snake venom, but the examiner rejected this argument on the ground that the compound was the same regardless of its use. The Board affirmed, concluding that a PHOSITA would have expected the claimed composition to neutralize the lethality of snake venom. The Federal Circuit reversed, holding that the Board erred in failing to consider rebuttal evidence offered by the applicant that the prior art discouraged the use of Fab fragments for this purpose. The court acknowledged *KSR* in a fleeting reference[251] after conceding that the record was sufficient to establish a prima facie case of obviousness. Without concluding that the Board's finding of obviousness was wrong, the Federal Circuit nonetheless vacated and remanded, holding that "the Board must give [the proffered rebuttal evidence] meaningful consideration before arriving at its conclusion."[252] Although it is treacherous to draw conclusions from one case, *In re Sullivan* suggests that the Federal Circuit may continue to set high standards for the PTO to document the basis for its obviousness rejections, even after *KSR*, making it costlier and more difficult to enter rejections.

There are, of course, also costs to a system that errs on the side of issuing patents that ultimately prove invalid. These costs are amplified in the context of drug patents because of the complex interplay between patents and drug regulation. While invalid patents keep generic competitors out of the market, consumers pay higher prices for drugs. But determining whether an invention would have been obvious at the time it was made is a complex task that takes time to do right. The more flexible and expansive the analysis, and the broader the range of evidence that can be considered, the longer it takes. The characterization of the nonobviousness conclusion as a question of law, subject to plenary review on appeal, further delays the ultimate day of reckoning. A paradoxical result of *KSR* may thus be to prolong the time it takes to clear invalid patents out of the marketplace, even when the challengers ultimately prevail.

VI. CONCLUSION

In pursuit of its mandate to make patent law more certain and predictable, and in order to ensure that the PTO and district courts evaluate patentability as of the time an invention was made without resort to hindsight, the Federal Circuit has deployed a variety of mechanisms to guide evaluations of (non)obviousness. In *KSR v. Teleflex*, the Supreme Court disapproved as unduly rigid the Federal Circuit's use of one of

[251] *Id.* at 1351.
[252] *Id.* at 1353.

these mechanisms, its "TSM" test, thereby calling into question other mechanisms that constrain the flexibility of the (non)obviousness inquiry. One such mechanism is the proof structure for evaluating the (non)obviousness of chemical and biopharmaceutical inventions, elaborated in a long line of cases from the CCPA and the Federal Circuit but never approved by the Supreme Court. The Federal Circuit has sometimes deployed this proof structure in a highly rigid and formalistic manner, especially in cases from the 1990s considering the (non)obviousness of claims to DNA sequences encoding known proteins. For the most part, however, it has used a more flexible analysis in evaluating the (non)obviousness of pharmaceutical patents. As a result, it has recently held many such patents invalid in the context of ANDA infringement litigation. Perhaps these cases, which are triggered by challenges to patent validity by generic competitors seeking regulatory approval to sell competing versions of successful products, reflect a selection bias in favor of weak patents, or perhaps the Federal Circuit has become suspicious that the pharmaceutical industry is improperly obtaining "evergreening" patents on trivial variations that do not involve true innovation. For whatever reason, it appears that in these cases the Federal Circuit has been using all along the flexible, market-sensitive analysis that the Supreme Court has commended to it in *KSR*. A review of these cases suggests that the pharmaceutical industry does indeed have a problem with the (non)obviousness test, but the problem is not *KSR*. The problem is that many of the patents it relies upon are invalid under time-honored patent doctrine, and with the benefit of a full evidentiary record, these patents cannot withstand validity challenges. But unless *KSR* permits the PTO to reject these claims in the first instance, on the basis of a more limited record, consumers will continue to pay premium prices on these products until challengers are able to demonstrate, under an expansive and flexible analysis, that the patents covering those products are invalid.