Expecting the Unexpected¹Mark A. Lemley²

Patent law rewards invention. Invention in turn means not merely that something is new, but that it is nonobvious—something that ordinary scientists in the field wouldn't have figured it out. We have a number of legal doctrines designed to decide whether an invention would be obvious to those in the field. One of the most important of those doctrines is the doctrine of “unexpected results.” If the patentee's invention produced unexpected results, the law says, that is pretty good evidence that it wasn't obvious.

A second important doctrine, established in the law only in 2007, is that if it is obvious to try to make something, and if those who might try would expect to succeed, making that thing is not patentable. After all, if an ordinary scientist would think to try a particular approach and would expect to succeed, actually doing so isn't really inventive. It's just the ordinary work we expect of scientists.

These two doctrines can conflict. What if it is obvious to try something, but actually trying it leads to unexpected results? This actually happens with some frequency, particularly in the chemical and pharmaceutical industries, where researchers are motivated to try various standard modifications of known chemicals but where the unpredictability of the art means that they can expect to be surprised by what they learn from time to time. Perhaps

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surprisingly, courts have not yet decided how to resolve this conflict, with a number of cases in the last several years preferring one doctrine or the other without directly acknowledging the conflict.

I argue that when these two legal doctrines conflict, the doctrine of unexpected results must give way. Obviousness is based on the idea that we should not give a patent if ordinary scientists could have gotten to the result without the encouragement of that patent.³ If researchers of ordinary skill were already motivated to try a new variation, and correctly expected that they would succeed, actually trying the new variation is normal science, not the extraordinary skill or insight required for invention. And if scientists would have created the new variation in the ordinary course of their duties, they would of necessity have stumbled upon the unexpected results. Normal science, not the incentive of a patent, led them to that course, so the invention is not patentable.

This result may alarm patent owners in the pharmaceutical industries, who have been obtaining patents for this sort of normal experimentation for years. But I think it is required by the Supreme Court's decision in *KSR*, which held that an invention was not patentable if it was

³ Abramowicz and Duffy argue that the role of nonobviousness is to identify those inventions that would not have occurred but for the promise of a patent and grant patents only to those inventions. Michael Abramowicz & John F. Duffy, *The Inducement Standard of Patentability*, 120 YALE L.J. 1590 (2011). I mostly, but not completely, agree with that formulation. Abramowicz and Duffy are correct that we should not grant patents to inventions that would be made without the grant of the patent; the grant of an exclusive right in such a case is social waste. But their inducement standard suggests that we might grant patents even to things that are not inventive if they are costly enough that no one will produce them without the promise of exclusivity. See also Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 503 (2009) (arguing for patent protection for old inventions in the pharmaceutical industry). Patent law does not currently protect the "sweat of the brow" unaccompanied by invention. *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). Other legal doctrines may create exclusivities to encourage companies to spend money on non-inventive activities; I discuss those ideas *infra*.

obvious to try.⁴ And while pharmaceutical patent owners may lament the loss of these patents, the rest of the world may not. Patents likely to be affected by the obvious-to-try rule tend to be follow-on patents used to try to extend the life of expired patents on new chemical entities, not breakthrough drugs that require strong protection.

I. The Law of Obviousness

A. The Primary Analysis

We grant patents only to inventions that are novel and nonobvious—ones that an ordinary scientist in the field would not have come up with. Obviousness is the “ultimate condition” of patentability—the single most significant doctrine dividing those ideas worth granting a patent on from run-of-the-mill work that does not deserve a patent.⁵ As the Supreme Court made clear in *KSR*, an ordinarily skilled researcher is “not an automaton,” but a scientist who is a problem-solver and will be motivated to improve things in the ordinary course of scientific work.⁶

The nonobviousness requirement—that inventions must, to qualify for a patent, be not simply new but sufficiently different that they would not have been obvious to the ordinarily skilled scientist—is in dispute in almost every case, and it is responsible for invalidating more

⁴ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

⁵ NON-OBVIOUSNESS: THE ULTIMATE CONDITION OF PATENTABILITY (John F. Witherspoon ed., 1980).

⁶ *Id.*

patents than any other patent rule.³ It is also perhaps the most vexing doctrine to apply, in significant part because the ultimate question of obviousness has an “I know it when I see it” quality that is hard to break down into objective elements.⁷

That hasn’t stopped the Federal Circuit from trying to find those objective elements. In the last quarter-century, the court has created a variety of rules designed to cabin the obviousness inquiry. Some of those rules—that an invention can’t be obvious unless there is a teaching, suggestion, or motivation to combine prior art elements or modify existing technology,⁸ and that an invention can’t be obvious merely because it is obvious to try⁹—were swept away by the Supreme Court in 2007. In *KSR*, the Court insisted on context-specific standards rather than rigid rules.¹⁰

B. Secondary Considerations (or Objective Evidence)

A second body of Federal Circuit obviousness precedent remained unchanged by *KSR*, however. Those cases involve the so-called “secondary considerations” or “objective evidence”

³ See John R. Allison & Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 AIPLA Q.J. 185, 209 tbl. 2 (1998); John R. Allison et al., *Understanding the Realities of Modern Patent Litigation*, 92 *Tex. L. Rev.* 769 (2014).

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⁷ Daralyn J. Durie & Mark A. Lemley, *A Realistic Approach to the Obviousness of Inventions*, 50 WM. & MARY L. REV. 989, 990 (2008). Portions of this paragraph and the next are adapted from that article.

⁸ See, e.g., *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002); *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); *Lindemann Maschinenfabrik GmbH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984).

⁹ See, e.g., *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

¹⁰ *KSR*, 550 U.S. at 421.

of nonobviousness.¹¹ While the basic obviousness inquiry is focused on what a hypothetical reasonable expert—the person having ordinary skill in the art, or PHOSITA¹²—would think is obvious, courts also consider real-world evidence about how the invention was received in the marketplace. These secondary considerations may include, for instance, whether the invention was a commercial success, whether others tried and failed to achieve it, and how the inventor was treated by the relevant scientific community.¹³ Secondary considerations have taken on greater significance since *KSR* as patentees have turned to them to try to overcome the stricter primary test of obviousness.¹⁴

¹¹ Whether you call them “secondary considerations” or “objective evidence” may depend on how much weight you want to give these factors. After all, “secondary considerations” are, well, secondary, while “objective evidence” sounds like the sort of decision-making criteria to which we all should aspire. Notably, the Supreme Court speaks of secondary considerations that “may have relevancy,” *Graham v. John Deere Co.*, 383 U.S. 2, 18 (1966), while the Federal Circuit prefers the term “objective evidence” and has elevated these considerations to a necessary part of the obviousness analysis, *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed.Cir.1983) (“[O]bjective evidence of nonobviousness . . . should when present always be considered as an integral part of the analysis.”); *Greenwood v. Haitori Seiko Co., Ltd.*, 900 F.2d 238, 241 (Fed. Cir. 1990). I will use the two terms interchangeably, doubtless to the chagrin of both sides.

¹² For discussion of the role of the PHOSITA in patent law, see, e.g., Rebecca S. Eisenberg, *Obvious to Whom? Evaluating Inventions from the Perspective of PHOSITA*, 19 BERKELEY TECH. L.J. 885 (2004); Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1185-90 (2002); John O. Tresansky, *PHOSITA--The Ubiquitous and Enigmatic Person in Patent Law*, 73 J. PAT. & TRADEMARK OFF. SOC'Y 37 (1991); see also ROBERT L. HARMON, PATENTS AND THE FEDERAL CIRCUIT § 4.3 (5th ed. 2001); Joseph P. Meara, Note, *Just Who is the Person Having Ordinary Skill in the Art? Patent Law's Mysterious Personage*, 77 WASH. L. REV. 267 (2002). The first known use of the term PHOSITA appears to be in Cyril A. Soans, *Some Absurd Presumptions in Patent Cases*, 10 IDEA 433, 438 (1966).

¹³ For discussion of those factors, see, for example, Rochelle Dreyfuss, *The Federal Circuit: A Case Study in Specialized Courts*, 64 N.Y.U. L. REV. 1 (1989); Robert P. Merges, *Economic Perspectives on Innovation: Patent Standards and Commercial Success*, 76 CAL. L. REV. 803 (1988); Edmund Kitch, *Graham v. John Deere Co.: New Standards for Patents*, 1966 SUP. CT. REV. 293.

¹⁴ See, e.g., Durie & Lemley, *supra* note 7; Natalie A. Thomas, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following KSR v. Teleflex*, 86 N.Y.U. L. REV. 2070, 2106 (2011).

For our purposes, the most important of the objective considerations is unexpected results. The paradigm case of unexpected results is *United States v. Adams*.¹⁵ Adams invented a just-add-water battery with a long shelf life that produced a stable current.¹⁶ Prior literature had indicated that the elements of the battery could not safely be combined together and might even explode.¹⁷ While the prior art disclosed each of the elements of Adams’s battery separately, the Court held that the combination of those elements was non-obvious, relying on the unexpected nature of his results to those of skill in the art.¹⁸ The fact that no one expected Adams’s battery to work meant that people of ordinary skill in the field wouldn’t try making it. That Adams did—and succeeded—was deserving of a patent.¹⁹

Adams was a case involving not only unexpected results, but also what patent law calls “teaching away” from the invention. It wasn’t just that the prior art didn’t expect Adams’s success, but that the prevailing wisdom told him not to bother trying. Indeed, he demonstrated his battery for Army experts, who refused to believe it could work even after seeing the results with their own eyes.²⁰ The rationale here seems straightforward: if the PHOSITAs thought that something wouldn’t work, and the patentee showed that, surprisingly, it

¹⁵ 383 U.S. 39 (1966).

¹⁶ *Id.* at 43.

¹⁷ *Id.* at 48.

¹⁸ *Id.* at 51-52.

¹⁹ See *KSR v. Teleflex*, 550 U.S. 398, 416 (2007) (describing *Adams* thus: “The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams’ design was not obvious to those skilled in the art.”).

²⁰ *Id.* at 43-44.

did, the patentee's discovery was likely not obvious to those PHOSITAS.²¹ Patentees frequently present evidence of their unexpected results, and the Federal Circuit has considered that evidence in a number of cases, essentially always as evidence in support of the patentee and a finding of nonobviousness.²² By contrast, the absence of a secondary consideration like unexpected results is not treated as evidence of obviousness. Instead, it is neutral.²³

C. Obvious to Try

While objective evidence of unexpected results can trace its pedigree at least as far back as the Supreme Court's 1966 decision in *Graham v. John Deere & Co.*,²⁴ the other doctrine of interest to us is of more recent vintage. That doctrine concerns what to do when it would be obvious to the PHOSITA to make a particular change to the prior art or test a new machine or compound. Scientists may be motivated to improve existing technology in a variety of standard ways without the need for a patent. Some of those improvements are simple linear thinking: e.g., if having one USB port on a computer is good, why not try having two? Others are optimization along lines known to be desirable: e.g., if raising battery life on a laptop from three to four hours is good, raising it to five hours should be even better.

²¹ As an aside, the law's reliance on unexpected results makes sense only if we think of the actual development and testing of an invention, rather than just a new idea, as central to what makes an invention. If the idea itself is all that matters, we shouldn't care whether or not it has unexpected results, something we learn only by implementing it. For an argument that the law should pay more attention to building and testing, not just thinking of an invention, see Mark A. Lemley, *Ready for Patenting*, __ **B.U. L. Rev.** __ (forthcoming 2016).

²² See, e.g., *Procter & Gamble Co. v. Teva Pharms. USA*, 566 F.3d 989, 995-98 (Fed. Cir. 2009); *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342 (Fed. Cir. 2012). Westlaw search for "unexpected results" in the Federal Circuit database on July 18, 2015 produced 369 opinions.

²³ See, e.g., *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986); *Medtronics, Inc. v. Intermedics, Inc.*, 799 F.2d 734, 739 (Fed. Cir. 1986).

²⁴ 383 U.S. 2, 18 (1966).

Just because ordinary scientists are motivated to try something doesn't mean they will succeed, however. It is obviously desirable to build a time machine²⁵ or to cure cancer, but that doesn't mean a scientist of ordinary skill would know how to do it. As the Federal Circuit put it, if "trying" simply means throwing darts at a combinatorial dartboard to see what sticks, getting the right answer is not obvious even if lots of people would like to get that answer.²⁶

The Federal Circuit originally drew from that logic the conclusion that obviousness to try was irrelevant—that it was not the proper test for obviousness. That mantra was repeated in a number of cases over a 25-year period.²⁷ But frankly it never made much sense. If something is obvious to try, scientists of ordinary skill will be motivated to try it. That doesn't mean they will succeed, of course, as the cancer example proves. But when obviousness to try a particular approach is coupled with a reasonable expectation of success, getting to the result is not inventive. It requires only doing what scientists in the field would both want and know how to do.²⁸ Put another way, we should distinguish between obvious *goals* – “increase battery life” or

²⁵ Well, except for the whole “killing your own grandmother” thing. *See, e.g.*, a large fraction of science fiction novels written in the last century; RENÉ BARJAVEL, *LE VOYAGEUR IMPRUDENT* (1948) (thought to be the first description of the grandfather paradox).

²⁶ *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (“[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.”).

²⁷ *See, e.g., In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) (“‘Obvious to try’ has long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.” (citation omitted)); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

²⁸ Some judges had pointed to the language in section 103 that “[p]atentability shall not be negated [sic] by the matter in which the invention is made” as a justification for rejecting obviousness to try. *Pfizer v. Apotex*, 488 F.3d 1377 (Fed. Cir. 2007) (Lourie, J., dissenting from denial of rehearing en banc). But that is a non sequitur. The reason an invention that is obvious to try is unpatentable is that the PHOSITA can be expected to produce it without the incentive of a patent, not because of the way the invention is made. The statutory language is in fact designed with a different purpose in mind – to permit patents on inventions made by accident. Congress adopted the language to reject the

“cure cancer” – and obvious *means* of achieving those goals. An obvious goal will motivate people to try new things, but that doesn’t mean the invention is obvious unless ordinary scientists would also have an obvious means of achieving those goals.

The Supreme Court so held in *KSR v. Teleflex* in 2007, overruling a quarter-century of Federal Circuit precedent that had rejected obviousness to try:

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “[o]bvious to try.” When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.²⁹

Thus, since 2007, the law has been that if it is obvious to try a particular set of solutions and scientists expect that one of them will work, people of ordinary skill will try them, and the resulting invention is not patentable because the process that produced it was obvious.³⁰

II. When Obvious to Try Leads to Unexpected Results

A. Why Does This Ever Happen?

KSR unintentionally set up a new conflict between the doctrines of obviousness to try and unexpected results. How should courts treat circumstances in which an invention is

controversial “flash of genius” test previously adopted by the Supreme Court in *A & P Tea Co. v. Supermarket Equipment Co.*, 340 U.S. 147 (1950), *See Graham*, 366 U.S. at ___ (documenting Congress’s rejection of the term “flash of genius”); Sean Seymore, *Serendipity*, 88 **N.C. L. Rev.** 185 (2009). And accidental inventions are surely not obvious to try; indeed, they aren’t “tried” at all.

²⁹ *KSR*, 550 U.S. at 321 (alteration in original).

³⁰ Curiously, some have denied that *KSR* changed the law. *See* Andrew V. Trask, *Obvious to Try: A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 **FORDHAM L. REV.** 2625 (2008).

obvious to try, and those who will try reasonably anticipate that they will succeed, but the resulting product has unexpected characteristics? Does the fact that scientists were motivated to produce the invention, and reasonably expected that they would succeed, mean that the invention is obvious? Or does the fact that when they did produce the predicted invention it had unexpected characteristics mean that it was not obvious?³¹

I should begin by explaining why this problem comes up at all. The reader might doubt that both of these things can be true at the same time. After all, if I know to try something, and I am reasonably confident it will work, why should the result be unexpected? One possibility, of course, is that I thought it would work but it didn't. That is an unexpected result, but not one that generally leads to a patent, because there is usually not much money in patenting failures.³²

A second possibility is that the technology is an uncertain one, so that the PHOSITA cannot always predict the effects of seemingly small changes. This has been true for some time in chemistry, for instance, particularly as the size of molecules increases. Chemists can often make small modifications to an existing chemical and produce an analogue with similar properties.³³ Sometimes, however, a small structural change results in a chemical with

³¹ Chris Cotropia has discussed a similar conflict, which he refers to as "type II predictability" – predictability as to results. Christopher A. Cotropia, *Predictability and Nonobviousness in Patent Law After KSR*, 20 MICH. TELECOMM. & TECH. L. REV. 391, 406-07 (2014). Cotropia focuses on his claim that courts and the PTO are misguided in relying on the ex post predictability of the effects of the invention once made as evidence of nonobviousness when they should be focusing on "type I predictability" – whether the inventor used the prior art predictably. *Id.* at 408-422. That is different, and in some sense the opposite, of the conflict I identify here, in which the desirability of building the invention is evident but the ultimate results are unexpected.

³² For an argument that we should patent failures, see Sean Seymore, *The Null Patent*, 53 Wm. & Mary L. Rev. 2041 (2012).

³³ As the Federal Circuit explained in *BMS v. Teva*, 752 F.3d 967 (Fed. Cir. 2014):

significantly different properties. Indeed, there is a whole body of case law devoted to this situation.³⁴

Finally, there are a number of circumstances in which a simple change known to those of skill in the art has the predictable, but not deterministic, possibility of producing different results. Most pharmaceutical compounds, for instance, are synthesized as a mixture of chemically distinct molecules called stereoisomers. The most common type of stereoisomerism results from so-called “chiral centers,” carbon atoms bonded to four different parts, which can be either “right-handed” (R) or “left-handed” (S).³⁵ When there is only one chiral center in a compound, there will be two stereoisomers that are mirror images of each other, called “enantiomers.”³⁶ Enantiomers contain the same atoms and have identical physical and

To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). Generally, an obviousness inquiry concerning such “known compounds” focuses on the identity of a “lead compound.” *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

A lead compound is a compound in the prior art that would be “a natural choice for further development efforts.” *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art. “[I]t is sufficient to show that the claimed and prior art compounds possess a ‘sufficiently close relationship . . . to create an expectation,’ in light of the totality of the prior art, that the new compound will have ‘similar properties’ to the old.” *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1293 (Fed. Cir. 2012) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

³⁴ Whether a lead compound and a claimed compound have a sufficiently close relationship frequently turns on their “structural similarities and differences.” *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010); *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1293 (Fed. Cir. 2012); *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc).

³⁵ ROBERT J. OUELLETTE & DAVID J. RAWN, ORGANIC CHEMISTRY: STRUCTURE, MECHANISM, AND SYNTHESIS 242-43 (2014).

³⁶ *Id.* at 243. Where there is more than one chiral center in a molecule, there will be more stereoisomers—for example, the RRS isomer and the RSR isomer—some of which may be mirror images

chemical properties, except that they rotate polarized light in opposite directions and react differently with other chiral molecules.³⁷ When the mixture of enantiomers is 50-50, it is known as a “racemic” mixture, and the separation into enantiomers or “racemates” is sometimes called a “chiral switch.”³⁸ Chemists long ago discovered that when a drug has effects in the very chiral environment that is the human body, it is often only one enantiomer of the drug that is doing the work, while the other is inert.³⁹ In that common case, removing the inert half of the mixture will, on average, double the effectiveness of the same dosage of the drug, because the modified drug will have only the effective bits and not the inert ones.⁴⁰ It is also sometimes the case that while, say, the negative enantiomer is responsible for the therapeutic benefits of the drug, the positive enantiomer is actually inhibiting those benefits, so removing the positive enantiomer from the racemic mixture will have a more-than-two-fold

of each other, but, if not, are called “diastereomers.” *Id.* at 254-55. Diastereomers frequently have different physical properties (melting points, solubility, reactivity, etc.) and are less interchangeable than enantiomers. *Id.* at 255. The following discussion will assume a simple case, where there is only one stereocenter and two mirror-image isomers.

³⁷ *Id.* at 245-46.

³⁸ *Id.* at 248-49; see also Israel Arganat, Hava Caner, & John Caldwell, *Putting Chirality to Work: The Strategy of Chiral Switches*, 1 NATURE REVIEWS 753, 753, 755 (2002) (describing the most financially successful chiral switch of all time—the racemic Prilosec (omeprazole) to the single-enantiomer Nexium (esomeprazole) just before Prilosec went off patent).

³⁹ As early as 1886, Arnaldo Piutti observed that the *l*-form of the amino acid asparagine was tasteless, while the *d*-form was sweet. Nevertheless, synthesizing enantiomerically pure drugs on a commercial scale wasn’t feasible until 1974, when William Knowles discovered a commercially viable way to make L-DOPA, for which he shared a Nobel Prize in 2001. Guo-Qiang Lin, Jian-Ge Zhang, & Jie-Fei Cheng, *Overview of Chirality and Chiral Drugs*, in CHIRAL DRUGS 4, 9-10 (Guo-Qiang Lin, Qi-Dong You, & Jie-Fei Cheng, eds. 2011). The chiral drug industry didn’t really take off until the 80s and 90s. *Id.* at 21-22.

⁴⁰ See Michael Eichelbaum & Annette S. Gross, *Stereochemical Aspects of Drug Action and Disposition*, 28 ADVANCES DRUG RES. 1, 7-8, 10 & tbl.2 (1996) (collecting examples of drugs where activity is mainly associated with one stereoisomer). For example, S-ofloxacin is more than 10 times as potent an antibiotic than R-ofloxacin. In a natural or an achiral synthetic environment, you will get racemic mixtures. Variations in mixture percentages happen when you are trying to make one enantiomer over the other, and not succeeding very well.

increase in the therapeutic effects of the drug.⁴¹ In rare cases, all the benefits will come from one enantiomer and all the side effects will come from the other.⁴²

In these latter two cases, the effect of separating the racemic mixture into enantiomers is “unexpected” in the sense that we could not have known in advance that there would be such a multiplier effect in this particular case. At the same time, scientists in the field were motivated to separate the enantiomers by the likelihood that there would be at least some substantial improvement in the efficacy of the drug,⁴³ so they were motivated to separate the mixture even apart from the possibility of a multiplier effect. They know how to separate the two; it is standard chemistry.⁴⁴ And because enantiomers normally have different properties,

⁴¹ For example, (R)-albuterol is a bronchodilator, but (S)-albuterol indirectly inhibits this activity. See Arganat et al., *supra* note 38, at 760. See also Eichelbaum & Gross, *supra* note 40, at 9 (describing how a number of 1,4-dihydropyridines elicit opposite effects on the same receptors).

⁴² For example, Plavix, (+)-methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate, is responsible for all the positive antiplatelet activity, whereas the negative isomer is responsible for all the neurotoxicity. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1081 (Fed. Cir. 2008). See also Eichelbaum, *supra* note 40, at 48 (describing how the side effects of racemic L-DOPA and D-penicillamine are entirely due to the inactive enantiomer).

⁴³ It is extremely common that drugs are more effective in one enantiomer than another? Indeed, it is rare that each enantiomer has equal effects. See Michael Eichelbaum & Annette S. Gross, *Stereochemical Aspects of Drug Action and Disposition*, 28 ADVANCES DRUG RES. 1, 4 (“The situation that both enantiomers are equipotent is rather seldomly encountered. In most cases differences in activity in either qualitative or quantitative terms are observed between enantiomers.”) Enantiomers would only have the same effect if the target binding site were achiral, and pretty much every molecule in your body of reasonable size is chiral. Certainly all proteins are.

⁴⁴ See, e.g., *Aventis Pharma Deutschland GmbH v. King Pharms., Inc.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (“Moreover, the ‘944 patent specifically taught that stereoisomers of ramipril “can be separated by conventional chromatographic or fractional crystallization methods.” ‘944 patent, col. 10, ll. 28–31. Aventis’s protestations notwithstanding, there is no evidence that separating 5(S) and SSSSR ramipril was outside the capability of an ordinarily skilled artisan.”).

By contrast, in the rare case in which the process of isolating the enantiomer is itself new and surprising, the invention may be patentable. See *Forest Labs., Inc. v. Ivax Pharms, Inc.*, 501 F.3d 1263, 1266 (Fed. Cir. 2007) (holding that resolving a racemic mixture of citalopram was not obvious because typical processes used to isolate enantiomers (like chiral HPLC) were known to fail, and that the method ultimately used as a last resort was one that “others of skill in the art would have similarly hesitated

they could reasonably expect to succeed in most cases in changing the characteristics of the racemic mixture, though not necessarily to succeed as well as they would if a multiplier effect was triggered. Further, they might also be motivated to try a chiral switch by the known—but uncertain—possibility of such a multiplier effect. In these cases, the chiral switch is obvious to try, but the actual effects of the switch may turn out to be unexpected.

B. Confusion in the Case Law

Courts since *KSR* have struggled with cases in which obviousness to try points in one direction and unexpected results in another. Those issues come up with particular frequency in cases involving enantiomers and other efforts to modify a known chemical compound in well-understood ways.

1. Cases Giving Primacy to Obviousness to Try

On the one hand, a number of cases have held that a modification of an existing chemical that is expected to have positive results is obvious to try, and therefore obvious, even if the results are better than expected. In *Hoffmann-La Roche Inc. v. Apotex, Inc.*,⁴⁵ for example, the Federal Circuit held that it was obvious to try a 150 mg once-monthly time-release dose of a chemical that was already being provided in a 5 mg daily dose, where the prior art included one reference disclosing the “total-dose concept” and a second reference establishing the optimal daily dose. When the monthly dose was actually tested, it turned out to have somewhat better bioavailability than a mere linear projection (5 mg per day x 30 days per month = 150 mg)

because there was a real possibility that the resolved intermediate would re-racemize during the attempt to convert it from the diol intermediate enantiomer to the desired citalopram enantiomer”).

⁴⁵ 748 F.3d 1326 (Fed. Cir. 2014).

would suggest. The patentee, Roche, argued that the nonlinear bioavailability of the drug was an unexpected result, but court said that “improved efficacy does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg. . . . The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected.”⁴⁶

Further, the motivation to produce an invention need not be the inventor’s motivation. If a PHOSITA would have reason to produce the new chemical, the fact that the inventor’s own motivation did not include an expectation of the particular result doesn’t matter. Thus, in *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc.*,⁴⁷ the patentee was surprised to learn that their combination of nanoparticles with an existing chemical eliminated the need to take the drug with food.⁴⁸ But the court held that that fact did not render the invention nonobvious because the PHOSITA would have been motivated to make the combination for a different reason – to decrease viscosity and reduce interpatient variability.⁴⁹ Thus, while the invention did have an unexpected result, it didn’t matter, because the PHOSITA would have made the invention anyway.

Hoffman-La Roche is the clearest statement in the Federal Circuit of the idea that obviousness to try coupled with a reasonable expectation of success outweighs the unexpected

⁴⁶ *Id.* at 1334 (citing *In re Merck & Co.*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (holding that a difference in degree of anticholinergic effect, which was not so “appreciable” that “the difference was really unexpected,” did not rebut the prima facie case of obviousness)). Notably, the *Merck* case, decided before *KSR* and obviousness to try, seems to point in a different direction than *Hoffman-La Roche*.

⁴⁷ 773 F.3d 1186 (Fed. Cir. Dec. 3, 2014).

⁴⁸ *Id.* at 1189, 1193.

⁴⁹ *Id.* at 1197-98.

nature of the results. But other Federal Circuit decisions have produced the same result, sometimes by concluding that if an invention was obvious to try and the PHOSITA reasonably expected it to succeed, succeeding could not be “unexpected.” Thus, in *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*,⁵⁰ the patent examiner had repeatedly rejected a combination of two known diabetes drugs as obvious to try, but on the fifth resubmission backed down in the face of a study with questionable statistical significance showing synergistic effects.⁵¹ The district court found that some synergistic effect would have been expected by the state of the art, and that the level of synergy reported by the plaintiff’s results was expected in view of the state of the art at the time.⁵² The Federal Circuit affirmed, saying the “unexpected results” actually were expected because synergy—some sort of non-linear benefit from combination—could itself be an expected result.⁵³ And in *Pfizer, Inc. v. Apotex, Inc.*,⁵⁴ while the panel did not directly discuss the tension between the two doctrines, it affirmed a finding of obviousness based on obviousness to try.⁵⁵ Three judges, dissenting from the court’s refusal to rehear the case en banc, felt that unexpected results trumped obviousness to try.⁵⁶

⁵⁰ 719 F.3d 1346 (Fed. Cir. 2013).

⁵¹ *Id.* at 1350-51.

⁵² *Id.* at 1352.

⁵³ *Id.* at 1155-56.

⁵⁴ 480 F.3d 1348 (Fed. Cir. 2007).

⁵⁵ *Id.* at 1367-68. While the (pre-*KSR*) court acknowledged that “obvious to try” was not a proper reason to invalidate a patent, it nevertheless proceeded to invalidate this one because it was the result of “routine testing.” *Id.*

⁵⁶ *Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1377 (Fed. Cir. May 2007) (denial of petition for rehearing). Now post-*KSR*, the dissenters felt that the panel did not properly defer to the district court’s finding of unexpected physical properties, and that those unexpected results rendered the patent valid. *Id.* at 1379-80, (Newman, J., dissenting); *Id.* at 1382-83 (Lourie, J., dissenting); *Id.* at 1383-84 (Rader, J., dissenting).

The Federal Circuit applied the primacy of obviousness to try to stereoisomers in *Aventis Pharma Deutschland GmbH v. King Pharms., Inc.*⁵⁷ There, the court held that

[I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is *prima facie* obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified. . . . Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified.⁵⁸

Aventis tried to argue that there were unexpected results due to increased potency.

Specifically, they argued that the substantially pure isomer claimed—the SSSSS isomer—is 18 times as potent as next most potent isomer—RRSSS. The Court said that increased potency as between the SSSSS and RRSSS isomers may well be unexpected, but the prior art was a mixture that did not include RRSSS isomer, and so *Aventis* had to show that the SSSSS isomer was unexpectedly more potent than that mixture, which it was not, because the SSSSS isomer was the only active component of that mixture.⁵⁹ In other words, once it was obvious to identify the active isomer from a mixture, the fact that that isomer had surprising properties on its own didn't matter, because those properties were already part of the known mixture.⁶⁰

To similar effect is *Bristol-Myers Squibb v. Teva*, a non-stereoisomer case.⁶¹ There, the court rejected a claim that a small modification to an existing chemical was patentable because

⁵⁷ 499 F.3d 1293 (Fed. Cir. 2007).

⁵⁸ *Id.* at 1301-02.

⁵⁹ *Id.* at 1302.

⁶⁰ See also *In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960), which held an enantiomer obvious in view of the racemate when it was “particularly expected” that the specific enantiomer would have the observed properties. *Id.* at 843.

⁶¹ 752 F.3d 967 (Fed. Cir. 2014).

the properties of the modified drug were unexpected. As the court explained, the PHOSITA understands that “a chemist in drug development would seek to make small, conservative changes to that structure. In drug development, it is common to modify a lead compound in an effort to obtain a compound with better activity.”⁶² While the modified drug later turned out to have unexpected properties, the court held that “[u]nexpected properties . . . do not necessarily guarantee that a new compound is nonobvious. While a ‘marked superiority’ in an expected property may be enough in some circumstances to render a compound patentable, a ‘mere difference in degree’ is insufficient.”⁶³ That is particularly true when, as here, the deficiency in the prior art that the new invention unexpectedly solved was not itself known at the time the patent was filed. If the PHOSITA would be motivated to make simple changes to the invention, the fact that those simple changes led to unpredicted results did not render the invention obvious. Three judges dissented from the refusal to take the case en banc, arguing that “an unexpected result or property is the touchstone of nonobviousness” and necessarily defeats an obviousness claim.⁶⁴

2. Cases Giving Primacy to Unexpected Results

At the same time, other Federal Circuit decisions have rejected obviousness to try when the results were unexpected. Often, these cases take the form of a conclusion that there were

⁶² *Id.* at 974 (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).

⁶³ *Id.* at 977 (citing *In re Papesch*, 315 F.2d 381, 392 (C.C.P.A. 1963); *In re Hoch*, 428 F.2d 1341, 1344 n.5 (C.C.P.A. 1970)).

⁶⁴ *Bristol-Myers Squibb Co. v. Teva Pharms. USA*, 769 F.3d 1339, (Fed. Cir. 2014) (Newman, J., dissenting from denial of rehearing en banc). A fourth judge dissented on different, narrower grounds. *Id.* at 1353-54 (Taranto, J., dissenting from denial of rehearing en banc).

too many choices to make it obvious to try any one of them. The unexpected results of the path taken are used as evidence to bolster the idea that there was no reasonable expectation of success in the first place. Thus, in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.*,⁶⁵ the challenger tried to argue that “techniques of homologation and ring walking would have been ‘obvious to try’” with respect to the patentee’s modification of the prior art compound.⁶⁶ The court rejected that argument: “Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.”⁶⁷ The compound patentees selected had negative properties and so was not the obvious choice. It also had unexpected results in terms of reduced toxicity, a fact the court used to bolster the conclusion that this was not the obvious compound to try.⁶⁸

Similarly, in *In re Rosuvastatin Calcium Litigation*,⁶⁹ the obviousness-to-try argument was explicitly overcome by proof of secondary considerations, including the unexpected result of reduced toxicity as compared to the lead compound, but also the fact that the prior art “taught away” from the invention:

⁶⁵ 492 F.3d 1350 (Fed. Cir. 2007).

⁶⁶ *Id.* at 1359.

⁶⁷ *Id.*

⁶⁸ *Id.* at 1361-62. For criticism of the lead compound doctrine as overly rigid and inconsistent with *KSR*, see Douglas L. Rogers, *Federal Circuit’s Obviousness Test for New Pharmaceutical Compounds: Gobbledygook?* (working paper August 25, 2014), available at <http://ssrn.com.abstract=2486559>.

One way to read *Takeda* is that because the prior art suggested there were negative properties of the compound, the case really involved teaching away and not merely unexpected results. But the court’s reasoning was not explicitly based on teaching away.

⁶⁹ 703 F.3d 511 (Fed. Cir. 2014).

We agree that ‘obvious to try’ was negated by the general skepticism concerning pyrimidine-based statins, the fact that other pharmaceutical companies had abandoned this general structure, and the evidence that the prior art taught a preference not for hydrophilic substituents but for lipophilic substituents at the C2 position.⁷⁰

Notably, the obvious-to-try argument here was a weak one. The accused infringer argued that insertion of a sulfonyl group at position C2 was one of a finite number of predictable solutions, but did not point to some specific reason the PHOSITA would try that particular combination.⁷¹

While none of these cases explicitly privilege unexpected results over obviousness to try, several Federal Circuit judges have proposed doing so in dissents. Judge Newman, dissenting in *Caraco*, argued that the discovery of the synergistic effect should have made combination nonobvious. She specifically expressed her view that obvious to try is limited to predictable results.⁷² She took the same view in dissenting from the denial of rehearing en

⁷⁰ *Id.* at 518.

⁷¹ *Id.*; *accord* *Leo Pharm. Products v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013). There, the Court found many pieces of objective evidence to defeat obviousness: (1) people had been trying to find shelf-stable steroid/vitamin D formulation for over a decade, (2) the prior art taught away from combining them for stability reasons, (3) the record included extensive evidence of unexpected results, and (4) none of the combination examples in the prior art were shelf-stable or acknowledged the stability problem. *Id.* at 1334-35. “Without more, and especially in the face of such strong objective indicia of nonobviousness discussed *infra*, the Board erred by using hindsight to determine that the addition of Serup’s or Dikstein’s vitamin D analog to Turi’s formulation would have been obvious. . . . Here, the objective indicia—taken in sum—are the most ‘probative evidence of nonobviousness . . . enabling the court to avert the trap of hindsight.’” *Id.* at 1356, 1359. Turning to obvious to try, the court held that combinations of more than eight different classes of additives and more than ten different categories of composition forms resulted in choices too broad for the invention to be obvious to try. *Id.* at 1356. The court noted the time lapse between the cited references, finding them to be background knowledge which did not even identify the problem, not a recitation of known, finite solutions to a problem. *Id.* at 1356-57. Furthermore, there was no reasonable expectation of success. *Id.* at 1357. *See also* *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (rejecting on the basis of unexpected results an “obvious-to-try” argument that was really just a hindsight application of common sense).

⁷² *Novo Nordisk A/S v. Caraco Pharm. Labs Ltd.*, 719 F.3d 1346, 1360 (Fed. Cir. 2013) (Newman, J., dissenting in part).

banc in *Pfizer, Inc. v. Apotex, Inc.*⁷³ Judge Lourie's and Judge Rader's dissenting opinions in that case also suggested that they thought obviousness to try had little application in a case with unexpected results.⁷⁴

Some enantiomer cases too have privileged unexpected results over obviousness to try. In *Sanofi-Synthelabo v. Apotex, Inc.*,⁷⁵ the court found that the patented dextrorotatory isomer⁷⁶ was not obvious in light of the known racemic mixture.⁷⁷ Racemates of two other thienopyridines had been resolved, and there was no observed advantage to separation in

⁷³ 488 F.3d 1377, 1378-80 (Fed. Cir. 2007) (Newman, J., dissenting from denial of rehearing en banc) ("The panel's application of the obvious-to-try standard is in direct conflict with precedent. . . . The panel further erred in declining to give weight to these acknowledged 'secondary considerations' of unexpected results.").

⁷⁴ *Id.* at 1382 (Lourie, J., dissenting from denial of rehearing en banc) (arguing that the panel failed to defer to the findings of fact made by the district court indicating that the salt's properties were unexpected); *Id.* at 1384 (Rader, J., dissenting from denial of rehearing en banc) ("'[O]bvious to try' jurisprudence has very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis."). Some commentators have taken this position as well. See, e.g., Scott R. Conley, *Irrational Behavior, Hindsight, and Patentability: Balancing the "Obvious to Try" Test With Unexpected Results*, 51 IDEA 271, 272 (2011) ("there must be a reasonable factor to rebut obviousness found through the "obvious to try" test. This factor should focus on significant unexpected results of the invention because if a result is truly unexpected, then the invention could not have been obvious."); Jonathan M. Spenner, *Obvious to Try Obviousness of Enantiomers in View of Pre- and Post-KSR Analysis*, 90 J. PAT. & TRADEMARK OFF. SOC'Y 475, 490 (2008) ("unexpected results can be used to show *retrospectively* that an invention would have been nonobvious even though it would have been considered obvious by a POSITA *prospectively* without the benefit of knowing the unexpected results.").

⁷⁵ 550 F.3d 1075 (Fed. Cir. 2008).

⁷⁶ Aside from differing interaction with other chiral molecules, the only observable difference between mirror-image stereoisomers is the direction in which they rotate plane-polarized light. The "dextrorotatory isomer" is the stereoisomer that rotates plane-polarized light to the right (also called the positive (+) enantiomer), and the "levorotatory isomer" is the stereoisomer that rotates plane-polarized light to the left (aka, the negative (-) enantiomer). This is why enantiomers are sometimes called "optical isomers"—an enantiomerically pure compound that rotates plane-polarized light is "optically active." OUELLETTE & RAWN, *supra* note 35, at 245-47.

⁷⁷ *Sanofi-Synthelabo*, 550 F.3d at 1090.

either case.⁷⁸ The chemical literature indicated at least ten separation techniques that could be tried, and Sanofi's actual approach—diastereomeric salt formation—required five months of experimenting with “diverse salt-forming compositions and conditions, in the hope of coming upon a lucky combination of reagents that will preferentially select one of the enantiomers and crystallize from the solution in optically pure form.”⁷⁹

Sanofi was the rare case in which the enantiomers ultimately patented exhibited “absolute stereoselectivity”—one isomer was responsible for all the therapeutic activity and the other was responsible for all the neurotoxicity. All the experts agreed that such absolute selectivity was rare and unpredictable. Usually, if one is more biologically active than the other, it causes both the therapeutic effects and side effects.⁸⁰ Thus, “a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. Clear error has not been shown in this finding, and in the conclusion of nonobviousness based thereon.”⁸¹ It affirmed the district court's conclusion that “[w]hether or not it may have been ‘obvious to try’ separating the enantiomers of PCR 4099 . . . , the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious.”⁸²

⁷⁸ *Id.* at 1081.

⁷⁹ *Id.*

⁸⁰ *Id.* at 1081.

⁸¹ *Id.* at 1087.

⁸² *Id.* at 1089.

III. Expecting the Unexpected

Both on the general question of the relationship between obviousness to try and unexpected results, then, and on the specific question of whether isolating enantiomers is obvious even if it produces a surprising result, Federal Circuit decisions in the eight years since *KSR* are directly at odds.⁸³ In this Part, I discuss how that conflict should be resolved.

The key to answering that question lies in the essential purpose of obviousness law. That purpose is to ensure that we grant patents only on inventions that the world would not otherwise obtain.⁸⁴ We don't grant patents on obvious inventions, not merely because doing so might prevent scientists from engaging in the normal course of their research,⁸⁵ but because if it is obvious to do something we shouldn't need the grant of a patent to induce people to do it. Denying patents to inventions that are obvious to try serves that purpose. If a PHOSITA is motivated to try to make an invention and has a clear path to success, the PHOSITA will try and will succeed without the incentive of a patent. The fact that that path led to unexpected results

⁸³ Cf. Rebecca S. Eisenberg, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 427 (2008) ("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.").

⁸⁴ Abramowicz & Duffy, *supra* note 3.

⁸⁵ See *Graham v. John Deere & Co.*, 383 U.S. 2, 6 (1966):

Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must "promote the Progress of . . . useful Arts."

is simply an added benefit. But it is not a benefit induced by the promise of a patent; the PHOSITA was going to try anyway. By contrast, unexpected results do not themselves deny that logic; they are merely evidence that hints that an invention was not well understood until it was made. Truly unexpected results may cause us to question whether the PHOSITA really had a reasonable expectation of success, and we should worry about hindsight bias in making that assessment.⁸⁶ Evidence that the prior art actually taught away from the invention may lead us to further question whether the invention was really obvious to try. But if they really did expect success (as in the enantiomer cases), scientists in the field would have produced the invention, unexpected results and all, without the incentive of a patent. Objective evidence of unexpected results in this sense really is a “secondary” consideration. It is indirect evidence we use to help predict what obviousness to try tells us directly: whether the PHOSITA would develop the invention without the promise of a patent. When the two are in conflict, then, obviousness to try should prevail as a matter of logic.⁸⁷

It is less clear that we should be happy with that result as a policy matter. In the pharmaceutical industry, where many of these issues arise, inventions may be expensive even if they are relatively certain. The development and testing of enantiomers to existing drugs is a straightforward scientific process, one that is obvious to try in light of the potential benefits of different isomers, but it can also be expensive and time-consuming, as the *Sanofi* example

⁸⁶ Conley, *supra* note __, at 271. For an experimental assessment of hindsight bias in obviousness, see Gregory Mandel, *Patently Nonobvious: Empirical Demonstration That the Hindsight Bias Renders Patent Decisions Irrational*, 67 OHIO ST. L. REV. 1371 (2006).

⁸⁷ By contrast, proper evidence of teaching away would discourage scientists from trying the invention, and therefore could rebut a case of obviousness to try.

described above illustrates.⁸⁸ More importantly, the process of getting FDA approval to sell a new drug is itself expensive and time-consuming even if the actual process of invention is not.⁸⁹ We generally don't need or want market exclusivity to encourage commercialization of ideas we already have,⁹⁰ but the pharmaceutical industry may be an exception.⁹¹ And empirical evidence suggests that pharmaceuticals are one of the few industries in which patents do more good than harm.⁹² We should be reluctant to deny patent protection to a significant class of pharmaceutical products.⁹³ And we might worry that even if it is obvious to try something and

⁸⁸ 550 F.3d 1075, 1081 (Fed. Cir. 2008).

⁸⁹ See Joseph A. DiMasi et al., *The price of innovation: new estimates of drug development costs*, 22 J. HEALTH ECON. 151, 166 (2003) (estimating the cost of a new drug to be \$800 million, unadjusted for inflation). Notably, that number includes substantial marketing costs, which arguably should not count.

⁹⁰ There is a substantial literature on the theory of patents as designed to encourage, not invention, but commercialization of existing knowledge. See Michael Abramowicz, *The Danger of Underdeveloped Patent Prospects*, 92 CORNELL L. REV. 1065, 1106 (2007) (identifying concern over sufficiently incentivizing commercialization); Michael Abramowicz & John F. Duffy, *Intellectual Property for Market Experimentation*, 83 N.Y.U. L. REV. 337, 339-40 (2008) (discussing interplay of intellectual property rights and market experimentation); F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697, 710 (2001) ("[A]lthough a simple reward for inventive effort might provide adequate incentives for invention itself, the nascent invention may never reach a single consumer without . . . incentives to commercialize."); Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 275-80 (1977) (exploring role played by patent system in securing returns on investment); Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341, 396 (2010) (proposing creation of "commercialization patents").

I have critiqued that claim elsewhere, see Mark A. Lemley, *The Myth of the Sole Inventor*, 110 MICH. L. REV. 709 (2012), and I won't repeat those criticisms here.

⁹¹ Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129, 130-32 (2004) (criticizing commercialization theory as "fundamentally anti-market," but noting that the regulatory barriers in the pharmaceutical industry make it the strongest candidate for application of that theory).

⁹² JAMES BESSEN & MICHAEL J. MEURER, *PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATION AT RISK* (2008).

⁹³ Conley worries that if pharmaceutical inventors are denied patents for doing the natural, logical thing, they will turn instead to irrational behavior or luck. Conley, *supra* note __, at 271-72. This is really a species of Roin's claim that we should grant them a patent for policy reasons even though the invention is in fact obvious, because otherwise they won't invest the time and money in commercializing the logical idea.

reasonable to expect success, scientists in industries like pharmaceuticals won't *actually* try the new thing if it is too expensive. For that reason, Ben Roin has argued that we should grant patents on obvious and even already-known inventions in the pharmaceutical industry.⁹⁴ His idea is to induce, not invention, but the commercialization of the invention once it has been made.

Nonetheless, I don't believe the economic characteristics of pharmaceutical inventions compel us to give a preference to unexpected results in cases where an invention is obvious to try. Patent law flirted with protecting things that are straightforward but expensive to develop in a series of biotechnology cases in the 1990s.⁹⁵ Those cases granted patents to human gene sequences identified from the amino acid sequence they expressed. That process was time-consuming—many possible gene sequences could have coded for any given amino acid sequence—but its outcome was predictable.⁹⁶ But once *KSR* was decided in 2007, the Federal Circuit overruled those cases, holding that they were inconsistent with the logic of obviousness

⁹⁴ Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 503 (2009); see also Eric Budish et al., *Do fixed patent terms distort innovation? Evidence from cancer clinical trials* (Oct. 21, 2012) (working paper) (on file with author); Jacob Sherkow, *Negating Invention*, 2011 B.Y.U. L. REV. 1091. Those who put existing drugs to a new use can already obtain a patent on that new use, but use patents are generally considered inferior to a patent on the chemical itself. See ROBERT P. MERGES & JOHN F. DUFFY, PATENT LAW AND POLICY (6th ed. 2013). But see Arti K. Rai & Grant Rice, *Use Patents Can Be Useful: The Case of Rescued Drugs*, 6 SCI. TRANSL. MED. 248fs30 (August 6, 2014) (arguing that use patents can nonetheless be valuable).

⁹⁵ *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995); *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993).

⁹⁶ Protein-synthesizing enzymes in the body determine which amino acid to use next by reading a three-base pair DNA sequence called a codon. There are 64 distinct codons that spell amino acids, but only 21 human amino acids. Thus, many possible gene sequences could code for a protein made up of many different amino acids. For a primer on the science, see ROBERT P. MERGES ET AL, INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE: 2015 CASE AND STATUTORY SUPPLEMENT Appendix A (2015). In *Bell*, the court noted that there were 10³⁶ possible gene sequences that could theoretically code for the human amino acid sequence Bell discovered. *Bell*, 991 F.2d at 785.

to try.⁹⁷ IP law more generally has rejected claims for protection of things that are not creative, but simply costly or a lot of work to produce. Copyright law, for instance, refuses to protect databases that lack creativity even if they are costly to compile.⁹⁸

The reason is that whatever the merits of exclusivity as compensation for the expense of producing something, it is fundamentally not what the patent system is about. The logic of Roin's argument is, at base, not an argument for a patent but for some form of non-patent regulatory exclusivity. Notably, it would apply not only to cases that led to unexpected results, but even to cases in which the enantiomer produced had perfectly predictable results. It is not invention that Roin would reward, but merely the act of going through the regulatory process.

Three final considerations lead me to conclude that denying patents to enantiomers or biotechnological inventions that are obvious to try should not worry us unduly as a policy matter. First, pharmaceuticals and biotechnology already do qualify for various forms of regulatory exclusivity outside the patent system. A new chemical entity – including a new enantiomer – approved by the FDA is entitled to five years of regulatory exclusivity regardless of what patent law provides.⁹⁹ That regulatory exclusivity is not subject to invalidation or any

⁹⁷ *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

⁹⁸ *Feist Publ'ns., Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340 (1991).

⁹⁹ 21 U.S.C. § 355(j)(5)(F)(ii):

If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section.

The FDA's interpretation of that provision is discussed at

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf>. See also 21 U.S.C. § 355(u) (providing that exclusivity specifically to single-enantiomer versions of

of the remedial limits of patent law. It can be extended beyond five years for various reasons, including pediatric testing or a small patient base.¹⁰⁰ Biological products gets even more protection—twelve years of data exclusivity before a biosimilar can seek FDA approval based on its similarity to an FDA-approved product.¹⁰¹ Several scholars have suggested that regulatory exclusivity, not patent law, is best suited to protecting heavily regulated industries like pharmaceuticals.¹⁰²

Second, the cost and delay associated with regulatory approval for follow-on drugs like enantiomers are substantially lower than for truly new chemical entities. In 1992, the FDA issued guidance encouraging NDA applicants to characterize each enantiomer and to develop

previously approved racemates as of 2007). See John R. Thomas, **Pharmaceutical Patent Law** (3d ed. Forthcoming 2016) (discussing section 355(u)); Israel Arganat, Hava Caner, & John Caldwell, *Putting Chirality to Work: The Strategy of Chiral Switches*, 1 NATURE REVIEWS 753, 755-56 (2002) (describing how, before FDAAA, FDA did not classify enantiomers of existing racemic drugs as new chemical entities (NCE), but categorized them on a case-by-case basis as new formulations or new derivatives (but never as a new molecular entity)); Kyle Faget, *Why FDCA Section 505(u) Should Not Concern Us Greatly*, 15 MICH. TELECOMM. TECH. L. REV. 453, 453-54 (2009) (describing how the Food and Drug Administration Act of 2007 allowed enantiomers of previously approved racemic mixtures to get five years of market exclusivity).

¹⁰⁰ 21 U.S.C. § 355A (offering six additional months of exclusivity in exchange for testing the effects of the drug on children); 21 C.F.R. § 316.31 (setting out requirements for obtaining seven years of exclusivity for “orphan drugs” that serve only a small patient population).

¹⁰¹ Biologics Price Competition and Innovation Act, 42 U.S.C. sec. 262(k).

¹⁰² See, e.g., Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007); John R. Thomas, *The End of “Patent Medicines”? Thoughts on the Rise of Regulatory Exclusivities*, __ FOOD & DRUG L.J. __ (forthcoming 2015); Jaime F. Cardenas-Navia, *Thirty Years of Flawed Incentives: An Empirical and Economic Analysis of Hatch-Waxman Patent Term Restoration*, 29 **Berkeley Tech. L.J.** 1301, 1376-81 (2014). For a discussion of the complex interrelationship between patent and regulatory exclusivity in encouraging invention, see Rebecca S. Eisenberg, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 **FORDHAM L. REV.** 477 (2003). Cf. Daniel J. Hemel & Lisa Larrimore Ouellete, *Beyond the Patents-Prizes Debate*, 92 **TEX. L. REV.** 303 (2013) (discussing the need to compare patents to other government efforts to promote innovation, albeit not including regulatory exclusivities).

single-enantiomer drugs.¹⁰³ That guidance indicates that "[t]o develop a single stereoisomer from a mixture that has already been studied non-clinically, an abbreviated, appropriate pharmacology/toxicology evaluation could be conducted to allow the existing knowledge of the racemate available to the sponsor to be applied to the pure stereoisomer. . . . If there is no difference between the toxicological profile of the single stereoisomeric product and the racemate, no further studies would be needed."¹⁰⁴ Thus, pharmaceutical companies that have already received FDA approval for a racemate do not need to restart the process with a full new drug application for an enantiomer, but instead can piggyback on the work they had already done for the racemate.

Finally, separate, later-filed patents on enantiomers, delayed-release versions, and other modifications of existing drugs arguably do more harm than good to society. They permit a practice known as "evergreening"—making minor modifications to existing drug patents in order to avoid facing generic competition as the basic patent on a drug expires.¹⁰⁵ Pharmaceutical patent owners use these new patents not to dramatically improve medical outcomes, but to produce what is essentially the same drug from the patient's perspective. But because current law often gives them a patent on the basis of a showing of unexpected results

¹⁰³ See FDA, *Development of New Stereoisomeric Drugs* (May 1, 1992), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm>.

¹⁰⁴ *Id.*

¹⁰⁵ For discussion of evergreening, see, e.g., Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. REV. 63 (2002); C. Scott Hemphill, *An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition*, 109 COLUM. L. REV. 629 (2009). Cf. Lisa Larrimore Ouellette, *How Many Patents Does It Take to Make a Drug? Follow-on Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299 (2010) (noting the rising number of patents per marketed drug); C. Scott Hemphill & Bhaven Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. EMPIRICAL L. STUD. 613 (2011) (same).

in these modifications, they can extend for years and even decades their ability to exclude generic competitors from the market. That is particularly true when patent owners couple these new patents with regulatory gaming strategies like “product-hopping,” taking the old version of the drug off the market as its patent expires and replacing it with the slightly modified form.¹⁰⁶ The benefit to society from the new version may be slight, but the reduction in competition can be substantial.¹⁰⁷ The obvious-to-try patents enabled by the unexpected results doctrine, then, are not the sort of pharmaceutical patents society should want to encourage.

This is not to say that we shouldn’t encourage pharmaceutical companies to identify and produce enantiomers. But the practice of first patenting a racemate and then separately patenting an enantiomer years later is problematic. Better to encourage pharmaceutical companies to identify the enantiomer that has the therapeutic benefit at the outset, rather than giving them extra patent life in exchange for waiting to do what was obvious for them to try.¹⁰⁸

¹⁰⁶ Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685 (2009); Herbert Hovenkamp et al., IP AND ANTITRUST §15.3b (discussing the law and economic effects of product hopping). Courts are beginning to find that product-hopping violates antitrust law. *New York ex rel Schneiderman v. Actavis PLC*, 787 F.3d 638 (2d Cir. 2015); *Abbott Labs v. Teva Pharms USA*, 432 F. Supp. 2d 408 (D. Del. 2006). *But see* *Mylan Pharms, Inc. v. Warner Chilcott PLC*, No. 12-3824, 2015 WL 1736957 (E.D. Pa. April 16, 2015) (rejecting product-hopping claim it (wrongly) viewed as novel). But it may well be profitable for a pharmaceutical company to engage in the practice even if it is later found to violate the antitrust laws. Antitrust judgments to date have been dwarfed by the profits the patentees stand to make by extending the life of their exclusivity with follow-on patents. *Cf.* Hemphill, *supra* note 105 (measuring the social cost of pay-for-delay settlements in the pharmaceutical industry).

¹⁰⁷ *Cf.* Rebecca S. Eisenberg, *Pharma’s Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 423-26 (2008) (arguing that many pharmaceutical patents were invalid even before *KSR* because they were follow-on patents directed to obvious variants of existing chemicals).

¹⁰⁸ The FDA has been encouraging applicants to investigate enantiomers in their initial filings. The result has been that more and more initial drug filings are enantiomers, not racemates. *See* Guo-Qiang

IV. Conclusion

There is a fundamental tension between two doctrines in patent law—obviousness to try and unexpected results. That tension has been reflected in a series of cases that are irreconcilably in conflict. I argue that when the two conflict, obviousness to try must prevail because it is consistent with the logic of obviousness doctrine. The result will be a blow to pharmaceutical patent owners who have come to rely on patents for inventions that are obvious to try. But in the long run it may be good for consumers as well as for the integrity of the patent system.

Lin, Jian-Ge Zhang, & Jie-Fei Cheng, *Overview of Chirality and Chiral Drugs*, in CHIRAL DRUGS 4, 9-10 (Guo-Qiang Lin, Qi-Dong You, & Jie-Fei Cheng, eds. 2011) (documenting the number of each type of chemical approved by the FDA).