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ESSAY

EXPECTING THE UNEXPECTED

*Mark A. Lemley**

Introduction

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 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 surprisingly, courts have not yet decided how to resolve this conflict, with a

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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.[1] 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 lacking the extra 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 outcome, 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 International Co. v. Teleflex Inc.*, which held that an invention was not patentable if it was obvious to try.[2] 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. And pharmaceutical patent owners may have other avenues to obtain protection they legitimately need.

Thinking about the tension between unexpected results and obviousness to try also offers a window on why we have an obviousness doctrine at all. *KSR*'s focus on obviousness to try may represent a fundamental shift in thinking about obviousness, from a focus on whether the result was expected to a focus on whether the process of getting to that result was conventional.

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1 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. *See* 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, 517–31 (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. *See 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 below.

2 KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

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.[3] 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.[4]

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 patents than any other patent rule.[5] 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.[6]

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.[7] 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 try[9]—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

3 Nonobviousness—The Ultimate Condition of Patentability (John F. Witherspoon ed., 1980).

4 *KSR*, 550 U.S. at 421.

5 *See* John R. Allison & Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 AIPLA Q.J. 185, 209 tbl.2 (1998); *cf.* John R. Allison et al., *Understanding the Realities of Modern Patent Litigation*, 92 Tex. L. Rev. 1769, 1782 (2014) (finding an equal number of invalidations on obviousness and anticipation grounds).

6 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.

7 *Id.*

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

considerations" or "objective evidence" 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 "PHOSITA"[12]—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]

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

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" seem, 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. 1, 18 (1966), while the Federal Circuit prefers the term "objective evidence" and has elevated these considerations to a necessary part of the obviousness analysis, *see* Greenwood v. Hattori Seiko Co., 900 F.2d 238, 241 (Fed. Cir. 1990); 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."). 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 for example Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1185–90 (2002); Rebecca S. Eisenberg, *Obvious to Whom? Evaluating Inventions from the Perspective of PHOSITA*, 19 BERKELEY TECH. L.J. 885 (2004); 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, *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 PAT. TRADEMARK & COPYRIGHT J. RES & ED. 433, 438 (1966).

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

14 *See, e.g.*, Durie & Lemley, *supra* note 6, at 996; Natalie A. Thomas, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following* KSR v. Teleflex, 86 N.Y.U. L. REV. 2070, 2083 (2011).

15 383 U.S. 39 (1966).

16 *Id.* at 43.

17 *Id.* at 47.

nonobvious, 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 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 large 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] Unexpected results are treated as a reason to treat the invention as nonobvious. In fact, however, they are more properly understood as indirect evidence that bears on the question of whether the PHOSITA would have been motivated to make the invention.

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

18 *Id.* at 51–52.

19 *See* KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (pointing to *Adams* and explaining that "[t]he 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 *Adams*, 383 U.S. at 43–44.

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*, 96 B.U. L. Rev. 1171 (2016).

22 *See, e.g.*, Kinetic Concepts, Inc. v. Smith & Nephew, Inc., 688 F.3d 1342, 1367–68 (Fed. Cir. 2012); Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 995–98 (Fed. Cir. 2009). A Westlaw search for "unexpected results" in the Federal Circuit database on Nov. 23, 2016, produced 387 opinions.

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

24 383 U.S. 1, 18 (1966).

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 the result of simple linear thinking that implements existing knowledge; for example, if having one USB port on a computer is good, why not try having two? Others are optimization based on goals known to be desirable even if the means is not; for example, if raising battery life on a laptop from three to four hours is good, raising it to five hours should be even better.

Just because ordinary scientists are motivated to try something doesn't mean they will succeed, however. It is obviously desirable to build a time machine[25] 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 twenty-five-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

25 Well, except for the whole "killing your own grandmother" thing. See for example RENÉ BARJAVEL, LE VOYAGEUR IMPRUDENT (1944) (thought to be the first description of the grandfather paradox), as well as a large fraction of science fiction novels written in the last century.

If you did invent a time machine, the question of when to patent it is actually a complicated one. *See, e.g.*, *U.S. Patent No. 1*, FUNAGAIN GAMES, https://www.funagain.com/control/product/~product_id=12373/~affil=BSFS (last visited Jan. 23, 2017) (describing a game designed by Falko Goettsch and James Ernst—the premise of which is that you have invented a time machine, but must now race back through time to patent it before other inventors of a time machine).

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." (emphasis added) (citation omitted) (citing *In re* O'Farrell, 853 F.2d 894, 903–04 (Fed. Cir. 1988))); *cf. id.* (stating that a reasonable expectation of success is all that is required for obviousness, but nonetheless rejecting obviousness to try).

28 Some judges had pointed to the language in 35 U.S.C. § 103 that "[p]atentability shall not be negatived [sic] by the manner in which the invention was made" as a justification for rejecting obviousness to try. Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377, 1383 (Fed.

another way, we should distinguish between obvious *goals*—such as to "increase battery life" or "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 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

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Cir. 2007) (Lourie, J., dissenting from denial of rehearing en banc) (first alteration in original) (internal quotation marks omitted) (quoting 35 U.S.C. § 103 (2012)). 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 controversial "flash of genius" test previously adopted by the Supreme Court in *Cuno Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 91 (1941). *See* Graham v. John Deere Co, 383 U.S. 1, 15 (1966) (documenting Congress's rejection of the term "flash of genius"); Sean B. Seymore, *Serendipity*, 88 N.C. L. Rev. 185, 190 & n.24 (2009) ("Congress inserted this language into § 103 of the 1952 Patent Act to put to rest the 'flash of genius' theory of patentability."). And truly accidental inventions are surely not obvious to try; indeed, they aren't "tried" at all. *See infra* notes 91–97 and accompanying text.

29 KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007) (alteration in original) (citations omitted).

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

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 sig-

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, 404–08 (2014). Cotropia focuses on his claim that courts and the Patent and Trademark Office (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 408–23. 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 disclose and record patent failures, see Sean B. Seymore, *The Null Patent*, 53 WM. & MARY L. REV. 2041 (2012); *cf.* Michal Shur-Ofry, *Access-to-Error*, 34 CARDOZO ARTS & ENT. L.J. 357 (2016) (arguing that the public should have access to failures that might otherwise be treated as trade secrets).

33 As the Federal Circuit explained in *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*:

> 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. Generally, an obviousness inquiry concerning such "known compounds" focuses on the identity of a "lead compound."
>
> A lead compound is a compound in the prior art that would be "a natural choice for further development efforts." 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."

752 F.3d 967, 973 (Fed. Cir. 2014) (citations omitted) (first quoting Eisai Co. Ltd. v. Dr. Reddu's Labs, Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008); then quoting Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009); and then quoting Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1293 (Fed. Cir. 2012)) (citing Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

nificantly different properties. Indeed, there is a whole body of caselaw 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.[35] 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).[36] When there is only one chiral center in a compound, there will be two stereoisomers that are mirror images of each other, called "enantiomers."[37] Enantiomers contain the same atoms and have identical physical and chemical properties, except that they rotate polarized light in opposite directions and react differently with other chiral molecules.[38] When the mixture of enantiomers is fifty-fifty, it is known as a "racemic" mixture, and the separation into enantiomers or "racemates" is sometimes called a "chiral switch."[39]

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.[40] 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

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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); *see also Otsuka*, 678 F.3d 1280, 1291 (Fed. Cir. 2012); *In re Dillon,* 919 F.2d 688, 700 (Fed. Cir. 1990) (en banc).

35 Lien Ai Nguyen et al., *Chiral Drugs: An Overview*, 2 INT'L J. BIOMEDICAL SCI. 85, 85 (2006).

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

37 *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 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.

38 *Id.* at 245–46.

39 *Id.* at 248–49; *see also* Israel Agranat et al., *Putting Chirality to Work: The Strategy of Chiral Switches*, 1 NATURE REVS. 753, 757 (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).

40 As early as 1886, Arnaldo Piutti observed that the *l*-form of the amino acid asparagine was tasteless, while the *d*-form was sweet. *See* Guo-Qiang Lin et al., *Overview of Chirality and Chiral Drugs*, *in* CHIRAL DRUGS: CHEMISTRY AND BIOLOGICAL ACTION 3, 4 (Guo-Qiang Lin et al. eds., 2011). 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. *Id.* at 9. The chiral drug industry didn't really take off until the 1980s and 1990s. *Id.* at 21–22.

have only the effective bits and not the inert ones.[41] 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 increase in the therapeutic effects of the drug.[42] In rare cases, all the benefits will come from one enantiomer and all the side effects will come from the other.[43]

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. Some enantiomers will have these effects, but not all will. And a smaller subset of enantiomers will have particular efficacy improvements. At the same time, scientists in the field are motivated to separate the enantiomers by the likelihood that there would be at least some substantial improvement in the efficacy of the drug,[44] so they are 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.[45] And because enantiomers normally have different properties, they could reasonably expect to succeed in most cases in

41 *See* Michel Eichelbaum & Annette S. Gross, *Stereochemical Aspects of Drug Action and Disposition*, *in* 28 ADVANCES IN DRUG RES. 1, 7–8, 10 tbl.2 (Bernard Testa & Urs A. Meyer eds., 1996) (collecting examples of drugs where activity is mainly associated with one stereoisomer). For example, S-ofloxacin is more than ten times as potent an antibiotic than R-ofloxacin. *Id.* at 10 tbl.2. 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.

42 For example, (R)-albuterol is a bronchodilator, but (S)-albuterol indirectly inhibits this activity. *See* Agranat et al., *supra* note 39, at 760; *see also* Eichelbaum & Gross, *supra* note 41, at 9 (describing how a number of 1,4-dihydropyridines elicit opposite effects on the same receptors).

43 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, 1077, 1081 (Fed. Cir. 2008); *see also* Eichelbaum & Gross, *supra* note 41, at 48 (describing how the side effects of racemic L-DOPA and D-penicillamine are entirely due to the inactive enantiomer).

44 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* Eichelbaum & Gross, *supra* note 41, at 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.

45 *See, e.g.*, Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 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.' Aventis's protestations notwithstanding, there is no evidence that separating 5(S) and SSSSR ramipril was outside the capability of an ordinarily skilled artisan." (citation omitted) (quoting U.S. Patent No. 5,348,944 col. 10, 11. 28–31 (issued Sept. 20, 1944))).

changing the characteristics of the racemic mixture, though not necessarily to succeed as well as they would if a multiplier effect were 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.[46]

B. Confusion in the Caselaw

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.*,[47] 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.[48] 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) would

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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 Pharm., Inc., 501 F.3d 1263, 1266, 1269 (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 [to use] 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").

46 Chris Holman argues that "there is no general expectation that separating a racemate into its constituent enantiomers will provide any benefit." Christopher M. Holman, *In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination* 50 Ind. L. Rev (forthcoming 2017) (manuscript at 15), https://papers.ssrn.com/sol3/papers2.cfm?abstract_id=2833983. But that seems to misunderstand the level of generality at which we should ask the scientific question. The benefits of enantiomers are uncertain. Sometimes they will have benefits and no costs; other times they will have costs and no benefits; and still other times they may have both. But the fact that any particular enantiomer might or might not provide a benefit shouldn't matter. The fact that enantiomers often do have benefits over racemates motivates scientists to try new ones to see if they confer such a benefit, just as the fact that a general area that is known to contain gold will motivate a search even though no one knows whether a particular plot of land will contain gold or not.

47 Hoffman-La Roche Inc. v. Apotex Inc., 748 F.3d 1326 (Fed. Cir. 2014).

48 *Id.* at 1332.

suggest.[49] The patentee, Roche, argued that the nonlinear bioavailability of the drug was an unexpected result, but the court said that:

> [I]mproved 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.[50]

Further, the inventor need not be motivated by the desire to produce the actual result, as long as he is motivated to do work that does in fact produce that result. 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.*,[51] the patentee was surprised to learn that its combination of nanoparticles with an existing chemical eliminated the need to take the drug with food.[52] 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.[53] 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 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 Pharmaceutical Laboratories, Ltd.*,[54] 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 that showed synergistic effects.[55] 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.[56] The Federal Circuit affirmed, saying the "unexpected results" actually were expected because syn-

49 *Id.* at 1334.

50 *Id.* (citation omitted) (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*.

51 Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186 (Fed. Cir. 2014).

52 *Id.* at 1189, 1193.

53 *Id.* at 1197–98.

54 719 F.3d 1346 (Fed. Cir. 2013).

55 *Id.* at 1349–51.

56 *Id.* at 1352.

ergy—some sort of non-linear benefit from combination—could itself be an expected result.[57] And in *Pfizer, Inc. v. Apotex, Inc.*,[58] while the panel did not directly discuss the tension between the two doctrines, it made a finding of obviousness on the basis of obviousness to try.[59] Three judges, dissenting from the court's refusal to rehear the case en banc, felt that unexpected results trumped obviousness to try.[60]

The Federal Circuit applied the primacy of obviousness to try to stereoisomers in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*[61] 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.[62]

Aventis tried to argue that there were unexpected results due to increased potency. Specifically, it argued that the substantially pure isomer claimed—the SSSSS isomer—is eighteen times as potent as the 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 the RRSSS isomer, and so Aventis had to show that the SSSSS isomer was unexpectedly more potent than that prior art mixture. It was not, because the SSSSS isomer was the only active component of the prior art mixture.[63] In other words, once it was obvious to identify the active isomer from a mixture, the fact that that isomer had surprising proper-

57 *Id.* at 1355–56.

58 Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007); *see also* Torrent Pharm. Ltd. v. Novartis AG, No. IPR2014-00784, at 15 (P.T.A.B. Sept. 24, 2015) ("[T]he fact that the inventors of the '283 patent may have discovered a new advantage of a combination of prior-art ingredients is not sufficient to render the claims of the '283 patent patentable, as long as there was some reason to combine the prior-art teachings that those ingredients should be used.").

59 *Pfizer, Inc.*, 480 F.3d at 1365–68. 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.*

60 Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377 (Fed. Cir. 2007) (denying 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).

61 Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293 (Fed. Cir. 2007).

62 *Id.* at 1301–02.

63 *Id.* at 1302.

ties on its own didn't matter, because those properties were already part of the known mixture.[64]

To similar effect is *Bristol-Myers Squibb v. Teva*, a non-stereoisomer case.[65] There, the court rejected a claim that a small modification to an existing chemical was patentable because 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.'"[66] 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."[67] 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.[68]

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 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.*,[69] the challenger tried to argue that "techniques of homologation and ring-walking would have been 'obvious to try'" with respect to the paten-

64 *See also In re* Adamson, 275 F.2d 952, 955 (C.C.P.A. 1960) (holding an enantiomer obvious in view of the racemate when it was "particularly expected" that the specific enantiomer would have the observed properties).

65 Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967 (Fed. Cir. 2014).

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

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

68 Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 769 F.3d 1339, 1350 (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).

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

tee's modification of the prior art compound.[70] 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."[71] The compound the 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.[72]

Similarly, in *In re Rosuvastatin Calcium Patent Litigation*,[73] 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:

> 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 C_2 position.[74]

Notably, the obvious-to-try argument here was a weak one. The accused infringer argued that insertion of a sylfonyl group at position C_2 was one of a finite number of predictable solutions, but did not point to some specific reason the PHOSITA would try that particular combination.[75]

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70 *Id.* at 1359.

71 *Id.*

72 *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?* (Ohio State Univ. Moritz Coll. of Law Pub. Law & Legal Theory Working Paper Series, Paper No. 271, 2015), 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.

73 *In re* Rosuvastatin Calcium Patent Litig., 703 F.3d 511 (Fed. Cir. 2012).

74 *Id.* at 518 (citation omitted) (citing *Takeda*, 492 F.3d at 1357).

75 *Id.*; *accord* Leo Pharm. Prods., Ltd. 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 a 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 . . . enabl[ing] the court to avert the trap of hindsight."

Id. at 1356, 1359 (alterations in original) (citations omitted) (quoting Crocs, Inc. v. Int'l Trade Comm'n, 598 F.3d 1294, 1310 (Fed. Cir. 2010)). Turning to "obvious to try," the

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.[76] She specifically expressed her view that "obvious to try" is limited to predictable results.[77] She took the same view in dissenting from the denial of rehearing en banc in *Pfizer, Inc. v. Apotex, Inc.*[78] 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.[79]

Some enantiomer cases, too, have privileged unexpected results over obviousness to try. In *Sanofi-Synthelabo v. Apotex, Inc.*,[80] the court found that the patented dextrorotatory isomer[81] was not obvious in light of the known

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 that 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).

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

77 *Id.*

78 488 F.3d 1377, 1379–80 (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.").

79 *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 a 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) ("[T]here 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 Chemical Enantiomers in View of Pre- and Post-*KSR *Analysis*, 90 J. PAT. & TRADEMARK OFF. SOC'Y 475, 491 (2008) ("[U]nexpected 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.").

80 550 F.3d 1075 (Fed. Cir. 2008).

81 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 (also known as the

racemic mixture.[82] Racemates of two other thienopyridines had been resolved, and there was no observed advantage to separation in either case.[83] The chemical literature indicated at least ten separation techniques that could be tried, and Sanofi's actual approach—diasteromeric 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."[84]

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.[85] All the experts agreed that such absolute selectivity was rare and unpredictable.[86] Usually, if one is more biologically active than the other, it causes both the therapeutic effects and side effects.[87] 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."[88] It affirmed the district court's conclusion that,

> Whether 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 anti-platelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious.[89]

C. Beyond Enantiomers

While enantiomers are an important example of the conflict between obviousness to try and unexpected results, they are not the only one. Another important class of pharmaceutical patents involves salts. A salt is a pH-neutral chemical, neither acidic nor basic. Many drugs are "free bases" that are basic rather than acidic. Some of those basic compounds have undesirable physical properties. As with enantiomers, inventors who discover a free base drug may therefore be motivated to identify salts of those drugs. The salt may have different chemical properties than the free base, but it

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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 36, at 245–47.

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

83 *Id.* at 1080.

84 *Id.* at 1081.

85 *Id.*

86 *Id.*

87 *Id.*

88 *Id.* at 1087.

89 *Id.* at 1089 (internal quotation marks omitted) (quoting Sanofi-Synthelabo v. Apotex Inc., 492 F. Supp. 2d 353, 392 (S.D.N.Y. 2007)).

turns out to be difficult to predict which salt forms will have which physical properties.[90]

Salts, then, present an issue similar to enantiomers: we know it will often be desirable to produce the salt form of a known chemical, but we can't predict exactly when a particular salt will have a particular benefit. The Federal Circuit held in *Pfizer, Inc. v. Apotex, Inc.* that a patent claim to "the besylate salt of amlodipine" was obvious to try where the prior art identified a number of candidate salts of the drug, but not besylate salt.[91] While the exact properties of the besylate salt were unpredictable, there was "a strong suggestion that any and all pharmaceutically-acceptable anions would form . . . salts and would work."[92] Nonetheless, many pharmaceutical patents are in the form of salts of existing compounds, and courts remain split over whether it is obvious to produce a particular salt.[93] The issues in the salt cases have important similarities to the enantiomer cases.

Nor is the conflict limited to chemical and pharmaceutical inventions. One might imagine any number of inventions whose result is a surprise but that were the product of a straightforward creative process designed to achieve some different result. There are plant patent cases that present the question because standard breeding techniques lead to surprising results.[94] Accidental inventions may also present the conflict in many cases. While a true accidental invention like Fleming's discovery of the medicinal properties of penicillin would not be something obvious to try, many accidental inventions are really discoveries of the unexpected property of something that was created for a different purpose.[95] The conflict may even arise with computer-generated inventions in which AI systems may produce surprising results while running established programs.[96] Any of those inventions might well be unpatentable under the obvious-to-try standard, since they would

90 Simon N. Black et al., *Structure, Solubility, Screening, and Synthesis of Molecular Salts*, 96 J. PHARMACEUTICAL SCI. 1053, 1053 (2007) ("[A]t present, the ability to predict which salt forms will have desirable physical properties is essentially nonexistent.").

91 Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1365 (Fed. Cir. 2007).

92 *Id.*

93 Valeant Int'l (Barbados) SRL v. Watson Pharm., Inc., No. 10-20526, 2011 U.S. Dist. LEXIS 128742, at *26 (S.D. Fla. 2011), *aff'd*, 534 F. App'x 999 (Fed. Cir. 2013) (finding a salt nonobvious because "salt selection is inherently unpredictable").

94 *See, e.g.*, *Ex parte* Wong, No. 93-3238, 1994 WL 1709498 (B.P.A.I. July 6, 1994). For a discussion of that case and how it would fare after *KSR*, see Mark D. Janis, Non-Obvious Plants 26–28 (2016) (unpublished manuscript) (on filed with author).

95 For a discussion of various examples, including the Post-It note, penicillin, vulcanized rubber, and the pacemaker, see Mark A. Lemley, *The Myth of the Sole Inventor*, 110 MICH. L. REV. 709, 733–34 (2012). For additional examples, including dynamite, the phonograph, X-rays, Teflon, and Velcro, see DEAN KEITH SIMONTON, ORIGINS OF GENIUS: DARWINIAN PERSPECTIVES ON CREATIVITY 35–36 (1999); *see also* Paul Thagard & David Croft, *Scientific Discovery and Technological Innovation: Ulcers, Dinosaur Extinction, and the Programming Language Java*, *in* MODEL-BASED REASONING IN SCIENTIFIC DISCOVERY 125, 126 (Lorenzo Magnani et al. eds., 1999).

96 *See* Ryan Abbott, *I Think, Therefore I Invent: Creative Computers and the Future of Patent Law*, 57 B.C. L. REV. 1079, 1081 (2016) (discussing the problem of inventions generated by

have been tried anyway. At the least, the patentee should have to show that the invention lay in recognizing the unexpected result, not in the mere generation of an easily-appreciated result by means of ordinary science.

III. Expecting the Unexpected

Both on the general question of the relationship between obviousness to try and unexpected results, 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.[97] In this Part, I discuss how that conflict should be resolved.

A. Obviousness to Try and the Purpose of Obviousness

The key to answering that question lies in understanding the essential purpose of obviousness law. That purpose is to ensure that we grant patents only on inventions the world would not otherwise obtain.[98] 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,[99] but because if scientists are already motivated to try 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 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.[100]

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computers and concluding that "being the first human to discover a computer's patentable result" should not be sufficient for patentability).

97 *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.").

98 Abramowicz & Duffy, *supra* note 1.

99 *See* Graham v. John Deere Co., 383 U.S. 1, 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.'" (quoting U.S. Const. art. I, § 8, cl. 8)).

100 While I have couched this argument in terms of inducement theory, the same result should obtain under Tim Holbrook's possession theory of obviousness. Holbrook explains that obviousness to try in fact demonstrates the public's constructive possession of the invention. Timothy R. Holbrook, *Patent Anticipation and Obviousness as Possession*, 65 Emory L.J. 987, 1035 (2016).

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. That doesn't mean they aren't a legitimate part of the obviousness inquiry. 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.[101] 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. That is most evident when, as sometimes happens, the unexpected results aren't even discovered until after the patent application is filed.[102] It seems hard to conclude, as some courts have, that unexpected results that weren't even known at the time of the patent application indicate a lack of motivation to try the patented invention.[103]

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. By contrast, proper evidence of teaching away would discourage scientists from trying the invention, and therefore could rebut a case of obviousness to try. Thus, new chemicals like enantiomers and salts that are known, variant types on existing drugs should be treated as presumptively obvious under the new law.[104]

One complication is the possibility that normal science itself depends on the incentives of patents for the results of that work, at least when those results are surprisingly good. Greg Mandel makes this argument. Gregory N. Mandel, *The Non-Obvious Problem: How the Indeterminate Nonobviousness Standard Produces Excessive Patent Grants*, 42 U.C. DAVIS L. REV. 57 (2008). But if that is true, it is the obviousness doctrine itself that would have to be revisited.

101 Conley, *supra* note 79, at 271. For an experimental assessment of hindsight bias in obviousness, see Gregory N. Mandel, *Patently Non-Obvious: Empirical Demonstration That the Hindsight Bias Renders Patent Decisions Irrational*, 67 OHIO ST. L.J. 1391 (2006).

102 *See, e.g.*, Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., 748 F.3d 1354, 1360 (Fed. Cir. 2014); Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1307 (Fed. Cir. 2011); *see also* SHASHANK UPADHYE, GENERIC PHARMACEUTICAL PATENT AND FDA LAW § 1.86 (2015 ed.).

103 *See* Douglas L. Rogers, *Obvious Confusion over Properties Discovered After a Patent Application*, 43 AIPLA Q.J. 489 (2015) (making this point).

Patent law sometimes encounters the opposite phenomenon—patent applications filed based on observed unexpected results that later prove inaccurate. For a discussion of the problems this creates, see Jacob Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. (forthcoming 2017).

104 *See* UPADHYE, *supra* note 102, § 1.87 (reaching this conclusion). As Upadhye points out, any enantiomer of a known drug will either have a different effect than the racemate or not, but that is a fact that is inherent to the enantiomer, not the product of invention.

I'm not sure it should matter whether the patent claims the unexpected result. It is true that many of the claims are to products standing alone and do not explicitly limit

So understood, *KSR* can be seen in broader context as part of a fundamental shift in how we think about obviousness. The pre-*KSR* chemical cases focus on whether the *product* of the inventive process would have been obvious to the PHOSITA. This explains the almost-exclusive focus on the structure of the resulting chemical, a focus that shows up not just in obviousness law but in other patent doctrines as well.[105] Unexpected results fit easily within that framework, because if the results are unexpected the inventive process produced a nonobvious end product. By contrast, *KSR* represents a shift in focus from the end product to the *process of producing* that product.[106] If the PHOSITA would be motivated to invent the claimed product, the fact that the thing produced is not what she anticipated shouldn't matter.[107] That conceptual focus may impact not just chemical cases, but cases involving accidental inventions as well.

B. Should Pharma Be Different?

It seems clear that obviousness to try trumps unexpected results as a matter of law and patent theory. 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 described above illustrates.[108] 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.[109] We generally don't need or want market exclusivity to encourage

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themselves to the unexpected result. But the scope of a claim shouldn't be affected by whether an inherent property of a chemical is or is not claimed. Any making or using of the chemical would infringe that element regardless. *See* Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371 (2005).

105 For instance, chemical patent law has historically required a "lead compound" as the focus for investigation and for the obviousness inquiry. *See, e.g.*, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). And written description cases in biotechnology focus on knowledge of the structure of a chemical, not its properties. *See, e.g.*, Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).

106 *See* Cotropia, *supra* note 31, at 393.

107 *See* Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("The Board seemed to believe that the 'reasonable expectation of success' inquiry looked to whether one would reasonably expect the prior art references to operate as those references intended once combined. That is not the correct inquiry . . . .").

108 550 F.3d 1075, 1081 (Fed. Cir. 2008).

109 *See, e.g.*, 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 $802 million, unadjusted for inflation). Notably, that number includes substantial marketing costs, which arguably should not count.

commercialization of ideas we already have,[110] but the pharmaceutical industry may be an exception.[111] Empirical evidence suggests that pharmaceuticals are one of the few industries in which patents do more good than harm.[112] We should be reluctant to deny patent protection to a significant class of pharmaceutical products.[113] And we might worry that even if it is obvious to try something and 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.[114] His idea is to induce not invention, but rather the commercialization of the invention once it has been made.[115]

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110 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 the 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 the role played by the 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); Mark A. Lemley & Robin Feldman, *Patent Licensing, Technology Transfer, and Innovation*, 106 AM. ECON. REV. 188, 190–91 (2016), and I won't repeat those criticisms here.

111 Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129, 139–41 (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).

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

113 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 79, 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.

114 *See* Roin, *supra* note 1, at 503; *see also* Jacob S. Sherkow, *Negativing Invention*, 2011 B.Y.U. L. REV. 1091; Eric Budish et al., *Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials* (Chicago Booth Research Paper No. 13-79, 2013), https://papers.ssrn.com/sol3/papers2.cfm?abstract_id=2353471. 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 PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY 231 (6th ed. 2013). *But see* Arti K. Rai & Grant Rice, *Use Patents Can Be Useful: The Case of Rescued Drugs*, 6 SCI. TRANSLATIONAL MED. 248 (2014) (arguing that use patents can nonetheless be valuable).

115 *See* Roin, *supra* note 1, at 503.

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.[116] 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.[117] But once *KSR* was decided in 2007, the Federal Circuit overruled those cases, holding that they were inconsistent with the logic of obviousness to try.[118] Intellectual property 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.[119]

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. That is a reasonable argument for regulatory intervention to help subsidize the pharmaceutical industry (or, alternatively, to make the process of FDA approval of drugs quicker and cheaper). But it is not, at base, an argument for granting a patent.

We do want people to find and produce enantiomers, at least in the cases where we can separate some of the side effects from the active ingredient effects. But 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

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

117 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 sixty-four distinct codons that spell amino acids, but only twenty-one 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 app. A (2015). In *Bell*, the court noted that there were 10^{36} possible gene sequences that could theoretically code for the human amino acid sequence Bell discovered. *Bell*, 991 F.2d at 784.

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

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

regardless of what patent law provides.[120] That regulatory exclusivity is not subject to invalidation or any 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.[121] Biological products get even more protection—twelve years of data exclusivity before a biosimilar can seek FDA approval based on its similarity to an FDA-approved product.[122] Several scholars have suggested that regulatory exclusivity, not patent law, is best suited to protecting heavily regulated industries like pharmaceuticals.[123] I think there are costs as well as benefits to regulatory exclusivity. But it seems a better conceptual fit for predictable but unexpected results than patent law.

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 appli-

120 21 U.S.C. § 355(j)(5)(F)(ii) (2012) ("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 FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, NEW CHEMICAL ENTITY EXCLUSIVITY DETERMINATIONS FOR CERTAIN FIXED-COMBINATION DRUG PRODUCTS: GUIDANCE FOR INDUSTRY (2014), 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 previously approved racemates as of 2007); JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW (3d ed. 2015) (discussing section 355(u)); Agranat et al., *supra* note 39, at 755–56 (describing how, before the Food and Drug Administration Amendments Act of 2007 (FDAAA), the 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 FDAAA allowed enantiomers of previously approved racemic mixtures to get five years of market exclusivity).

121 21 U.S.C. § 355(a)–(b) (offering six additional months of exclusivity in exchange for testing the effects of the drug on children); 21 C.F.R. § 316.31 (2015) (setting out requirements for obtaining seven years of exclusivity for "orphan drugs" that serve only a small patient population).

122 Biologics Price Competition and Innovation Act, 42 U.S.C. § 262(k) (2012).

123 *See, e.g.*, Jaime F. Cárdenas-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); 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*, 70 FOOD & DRUG L.J. 39 (2015). 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 L. Ouellette, *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).

cants to characterize each enantiomer and to develop single-enantiomer drugs.[124] That guidance indicates that:

> To 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.[125]

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 in finding the optimal enantiomer. And the government itself motivates them to do so.

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.[126] While patent law theoretically prohibits "double patenting"—obtaining more than one patent on the same invention[127]—in practice pharmaceutical companies often obtain follow-on patents on trivial variants of their basic chemical once the initial patent is about to expire.[128] 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 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 gam-

124 *See Development of New Stereoisomeric Drugs*, U.S. Food & Drug Admin. (May 1, 1992), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm.

125 *Id.*

126 For a discussion of evergreening, see for example C. Scott Hemphill, *An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition*, 109 Colum. L. Rev. 629 (2009); Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. Rev. 63 (2004); *cf.* C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. Empirical L. Stud. 613 (2011) (noting the rising number of patents per marketed drug); Lisa L. Ouellette, Note, *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) (same).

127 *See, e.g.*, Miller v. Eagle Mfg. Co., 151 U.S. 186 (1894); *In re* Vogel, 422 F.2d 438 (C.C.P.A. 1970).

128 For discussion of this practice and criticism of the narrow modern application of the double-patenting doctrine, see Douglas L. Rogers, *Double Patenting: Follow-On Pharmaceutical Patents that Suppress Competition* (Ohio State Univ. Moritz Coll. of Law Pub. Law & Legal Theory Working Paper Series, Paper No. 324, 2016), https://ssrn.com/abstract=2709067.

ing 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.[129] The benefit to society from the new version may be slight, but the reduction in competition can be substantial.[130] The obvious-to-try patents enabled by the unexpected results doctrine, then, are not the sort of pharmaceutical patents society should 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. It is 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.[131]

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.

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129 HERBERT HOVENKAMP ET AL., IP AND ANTITRUST: AN ANALYSIS OF ANTITRUST PRINCIPLES APPLIED TO INTELLECTUAL PROPERTY LAW § 15.3c1 (2002) (discussing the law and economic effects of product-hopping); Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685 (2009). Courts are beginning to find that product-hopping violates antitrust law. *See* New York *ex rel* Schneiderman v. Actavis PLC, 787 F.3d 638 (2d Cir. 2015); Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408 (D. Del. 2006). *But see* Mylan Pharm., Inc. v. Warner Chilcott PLC, No. 12-3824, 2015 WL 1736957 (E.D. Pa. 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 126 (measuring the social cost of pay-for-delay settlements in the pharmaceutical industry).

130 *Cf.* Eisenberg, *supra* note 97, at 423–28 (arguing that many pharmaceutical patents were invalid even before *KSR* because they were follow-on patents directed to obvious variants of existing chemicals).

131 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* Lin et al., *supra* note 40, at 4, 9–10 (documenting the number of each type of chemical approved by the FDA).