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## Why FDCA Section 505(U) Should Not Concern us Greatly

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## COMMENT

# WHY FDCA SECTION 505(U) SHOULD NOT CONCERN US GREATLY

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## INTRODUCTION

Among the many amendments found in the Food and Drug Administration Amendment Act of 2007 (FDAAA) is a provision at the end of the act, Section 505(u), which grants chiral switches five years of market exclusivity under certain circumstances.<sup>1</sup> Prior to Congressional enactment of the FDAAA, the Food and Drug Administration (FDA) refused to award new chemical entity (NCE) status to enantiomers of previously approved racemic mixtures.<sup>2</sup> The FDA defines a new chemical entity (“NCE”) as a drug that contains no active moiety that has been approved by the FDA in any other application submitted under Section 505(b) of the FDCA.<sup>3</sup> According to the FDA, NCEs are by definition innovative and represent significant changes from already-approved drug products,

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1. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified at 21 U.S.C. § 355(u) (2007)).

2. A racemic mixture is one which consists of both pairs of enantiomers. David M. Gersten, *The Question for Market Exclusivity in Biotechnology: Navigating the Patent Minefield*, 2 NEURORX: J. AM. SOC’Y FOR EXPERIMENTAL NEUROTHERAPEUTICS 572, 575 (2005). Enantiomers are sometimes referred to as optical isomers or stereoisomers. Regardless of the terminology used, these are molecules that are identical in atomic constitution and bonding, but which only differ with respect to the three dimensional arrangements of atoms. *Id.* at n.30.

3. Center for Drug Evaluation and Research, Frequently Asked Questions for New Drug Product Exclusivity, <http://www.fda.gov/cder/about/smallbiz/exclusivity.htm> (last visited Mar. 16, 2009). An active moiety is the molecule or ion responsible for the physiological or pharmacological activity of a drug. *Id.*

such as a new use.<sup>4</sup> Granting five years of market exclusivity to chiral switches mimics the exclusivity accorded to NCEs. This policy change may be rewarding innovation that has either gone unrecognized as patentable by the Federal Circuit or has been recognized as patentable under a unique set of qualifying standards by the Federal Circuit.<sup>5</sup> From this perspective, it may appear as though Congress, by enacting Section 505(u), has somehow done an end-run around the patent system by allowing exclusivity where none has been previously offered. This Comment, however, argues that Section 505(u) will have a limited effect on drug development incentives and generic entrance into the marketplace because the ease with which most racemic mixtures may be resolved and the need for developing safe drugs in the first instance to gain FDA market approval points away from continued development of racemic drugs.<sup>6</sup> In other words, Section 505(u) is time-limited because drug companies today are almost exclusively pursuing single enantiomer drugs.

### I. ENANTIOMERS AND CHIRALITY: A BRIEF REVIEW

In general, chirality describes objects which possess non-superimposable mirror images. Many objects are chiral, and perhaps the most common examples of chiral objects are one's left and right hands. In chemistry, chirality refers to a class of molecules known as enantiomers, or optical isomers, which display the same type of handedness as one may observe when looking at one's own hands. These mirror image, or chiral, molecules share all of the same atoms and molecular properties, such as melting point, density, boiling point, and chemical reactivity.<sup>7</sup> Aside from the geometric arrangement of atoms around a stereogenic center resulting in non-superimposable mirror images, these molecules differ only insofar as they rotate the plane of polarized light in opposite directions.<sup>8</sup>

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4. *Id.*

5. *See infra* Parts II–III.

6. Wilson H. De Camp, *The FDA Perspective on the Development of Stereoisomers*, 1 *CHIRALITY* 2, 2 (1989) (noting how the difficulty of resolving racemates was overcome in the 1970s when high-performance liquid chromatography was developed); Michael Strong, *FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer More Effective Drugs*, 54 *FOOD & DRUG L.J.* 463, 467–68 (1999) (noting how improvements in separation methods have made development of single enantiomer drugs more feasible).

7. De Camp, *supra* note 6, at 3; Gersten, *supra* note 2, at n.30.

8. De Camp, *supra* note 6, at 3; Gersten, *supra* note 2, at n.30; Strong, *supra* note 6, at 466.

Biological systems are notorious for being handed themselves, in that they are sensitive to enantiomers.<sup>9</sup> If I hold out my left hand to shake your hand, you would shake my hand with your left hand, not your right. Receptors inside the human body discriminate in much the same way. So, for example, receptors prefer one enantiomer to the other—the body's receptors shake hands with the chiral molecule much like humans shake hands.<sup>10</sup> Unfortunately for scientists trying to develop drugs, synthesis of drugs often produces a mixture of both *R* and *S* enantiomers, a racemic mixture.<sup>11</sup> From there, it is up to a developing firm whether or not to pursue separation of the paired enantiomers when developing a given drug.

Enantiomers have had a large impact on drug research, design, and development.<sup>12</sup> This effect is not surprising given the advantages conferred by many single enantiomer drugs. Elimination of the paired enantiomer in the racemic mixture may result in nullification of toxic side effects<sup>13</sup> and antagonistic effects on the active enantiomer.<sup>14</sup> Moreover, many single enantiomer drugs display reduction of the total administered dose, an enhanced therapeutic window, reduction of inter-subject variability and a more precise estimation of dose-response relationships.<sup>15</sup> Provided separation of the paired enantiomer is feasible, there are significant advantages to developing a drug in enantiomeric form.<sup>16</sup>

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9. See American Medical Association, Geometric Isomerism and Chirality: The USAN Perspective, <http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/ united-states-adopted-names-council/naming-guidelines/geometric-isomerism-chirality-the-usan-perspective.shtml> [hereinafter *The USAN Perspective*].

10. See *id.*

11. See De Camp, *supra* note 6, at 2; Barnaby Feder, *Business Technology*; *Separating "Mirror" Molecules for Better Drugs*, N.Y. TIMES, Feb. 12, 1992, at D7.

12. See Israel Agranat & Hava Caner, *Intellectual Property and Chirality of Drugs*, DRUG DISCOVERY TODAY, July 1999, at 313; see also Angelo DePalma, *Chirality Companies Broaden Their Approaches*, GENETIC ENGINEERING NEWS, May 1, 2001, at 1.

13. Although arguably unavoidable, most people attribute the largest enantiomer debacle to the thalidomide scare of the 1960s. See De Camp, *supra* note 6, at 4; see also Widukind Lenz, *Thalidomide and Congenital Abnormalities*, 279 LANCET 271, 271–72 (1962).

14. See Hava Caner et al., *Trends in the Development of Chiral Drugs*, DRUG DISCOVERY TODAY, Feb. 2004, at 105.

15. *Id.*

16. See, e.g., Dean A. Handley, *The Therapeutic Advantages Achieved Through Single-Isomer Drugs*, 6 PHARMACEUTICAL NEWS 11 (1999) (noting that therapeutic advantages over racemates are often observed in the corresponding single enantiomer drug).

## II. FDA POSITION ON ENANTIOMERS PRE-FDAAA

Given the advantages of single enantiomer drugs over their racemic counterparts, it is not surprising that the FDA issued a policy statement expressing a preference for single enantiomer drugs.<sup>17</sup> Though drug companies are not formally required to pursue development of single-enantiomer drugs, the FDA asked that applicants recognize the existence of chirality when developing new drugs. Specifically, the FDA asked that drug developers attempt separation of enantiomers and assess the pharmacokinetic contribution of each enantiomer.<sup>18</sup> Moreover, the FDA noted that “[i]f toxicity of significant concern can be eliminated by development of single isomer [sic] with the desired pharmacologic effect, it would in general be desirable to do so.”<sup>19</sup> Manufacturers were urged to contact the FDA with questions about the “definition of ‘significant toxicity.’”<sup>20</sup>

Not only did drug companies undertake developing new drugs as single-enantiomers, but some companies undertook development of a single-enantiomer drugs from a previously approved racemates, a conversion referred to as “chiral switching”.<sup>21</sup> Despite expressing a general preference for single-enantiomer drugs, the FDA would not grant chiral switches new chemical entity status.<sup>22</sup> Because the FDA concluded that the active moiety (or active ingredient) of both the single-enantiomer and the racemate was the same, the single-enantiomer was not new for the purposes of FDA marketing exclusivity provisions.<sup>23</sup> Nonetheless, mar-

17. FDA’s Policy Statement for the Development of New Stereoisomeric Drugs, 57 Fed. Reg. 22,249 (May 27, 1992), available at <http://www.fda.gov/cder/guidance/stereo.htm> [hereinafter New Stereoisomer Drugs Policy].

18. *Id.*; Caner et al., *supra* note 14. See Israel Agranat et al., *Putting Chirality to Work: The Strategy of Chiral Switches*, 1 NATURE REV.: DRUG DISCOVERY 753, 754 (2002).

19. New Stereoisomer Drugs Policy, *supra* note 17.

20. *Id.*

21. Geoffrey Tucker, *Chiral Switches*, 355 LANCET 1085 (2000).

22. See Policy on Period of Marketing Exclusivity for Newly Approved Drug Products with Enantiomer Active Ingredients: Request for Comments, 62 Fed. Reg. 2167, 2168 (Jan. 15, 1997) [hereinafter Enantiomer Exclusivity Request for Comments]; Strong, *supra* note 6, at 480. The FDA defines “new chemical entity” as a drug containing no active moiety that has been approved by the FDA in any other application submitted under Section 505(b) of the FDCA. The FDA’s longstanding interpretation of the term “new molecular entity” requires that a compound contain an entirely new active moiety. DONALD O. BEERS, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* app. 34–75 (Aspen Publishers ed., 6th ed. 2004).

23. “FDA notes that a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity.” Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,898 (July 10, 1989). See Agranat et al., *supra* note 18, at 755.

keting of new, single-enantiomer drugs with a previously-approved racemate still required FDA approval.<sup>24</sup>

Absent a patent on the single-enantiomer version of a given drug, the FDA offered only limited market protection to pharmaceutical companies undertaking chiral switches. For example, the FDA would grant three years of marketing exclusivity when additional clinical trials were necessary for market approval.<sup>25</sup> However, requirements for market approval of single-enantiomer drugs resulting from chiral switches were relaxed as compared to those for newly-developed drugs or new chemical entities. For instance, the FDA allowed sponsors of single-enantiomer drugs to rely on toxicity reports from the parent racemate rather than generating new toxicity reports on the single-enantiomer in some circumstances.<sup>26</sup> Moreover, the FDA initially seemed somewhat willing to forego exhaustive phase III clinical studies.<sup>27</sup> Industry leaders, however, anticipated approval of single-enantiomer drugs with a previously approved racemate as requiring nearly full-scale clinical trials in circumstances where the single-enantiomer drug claimed improved safety and efficacy or new indications.<sup>28</sup>

Because the FDA considered market approval of single-enantiomer drugs resulting from chiral switching on a case-by-case basis, approaching drug development with certainty about returns on investment was seemingly impossible. Because drugs are capable of generating billions of dollars per year in sales during periods of market exclusivity,<sup>29</sup> it is easy to see why innovator companies would want FDA market exclusivity in return for engaging in the uncertain process of single-enantiomer development. However, granting FDA market exclusivity for purifying a racemate would keep generic drugs off the market beyond any patent term garnered from developing the original racemate or the derivative, single-enantiomer. Without FDA NCE exclusivity forthcoming, drug companies were incentivized to pursue market exclusivity of purified racemates or single-enantiomers via the patent system.<sup>30</sup>

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24. 21 U.S.C. § 355(a) (2006); *see also* Strong, *supra* note 6, at 480–82.

25. 21 U.S.C. § 355(c)(3)(E).

26. Steven C. Carlson, *The Case Against Market Exclusivity for Purified Enantiomers of Approved Drugs*, 1 YALE SYMP. L. & TECH. 6, 8 (1999).

27. *Id.* (noting that required clinical trials on single enantiomer drugs with a previously-approved racemate would take four to six years rather than the customary ten to fourteen for pioneer drugs).

28. Strong, *supra* note 6, at 480 (citing Sol Barer, Celgene CEO).

29. Erica Pascal, *The Billion Dollar Naming Game: How Ambiguities in Patent Term Extension Provisions Allow Companies to Add Billions of Dollars to the Bottom Line*, 24 BIOTECHNOLOGY L. REP. 547, 547 (2005).

30. *See* 21 U.S.C. §§ 505(c)(3)(E)(ii), 505(j)(5)(F)(ii) (2006) (illustrating that the FDA had declined to grant NCE exclusivity to enantiomers that were part of previously-approved racemic mixtures); *see also* 54 Fed. Reg. 28872, 28898 (July 10, 1989) (noting that the FDA

### III. UNCERTAINTY ACCOMPANIES PATENTING ENANTIOMERS

Chemists have been trying to untangle the puzzle presented by enantiomers since the 1800s, when Louis Pasteur discovered the optical isomerism of tartaric acid.<sup>31</sup> Producing a mixture containing a single enantiomer required Pasteur to separate the crystallized enantiomers by hand.<sup>32</sup> Today, teasing apart enantiomers or resolving the compound into its constituent enantiomers can be easier or harder depending on the number of stereogenic centers present in a given molecule. The number of possible enantiomer pairs increases as the number of stereogenic centers increases.<sup>33</sup> With the advent of advanced chromatographic methods in the 1970s, such as High Performance Liquid Chromatography (HPLC),<sup>34</sup> scientists no longer crystallize compounds and separate enantiomers by hand as Pasteur did long ago.<sup>35</sup> Utilized extensively by analytical chemists, HPLC is a type of column chromatography used to separate molecules.<sup>36</sup> Because HPLC has rendered resolving compounds almost routine,<sup>37</sup> whether or not enantiomers should be patentable after the racemate has been patented—a chiral switch—remains an open question.<sup>38</sup>

The United States Constitution grants Congress the authority “to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective

need not grant exclusivity to purified enantiomers because the racemate, and by extension the enantiomer, had already been approved).

31. John Caldwell, *Do Single Enantiomers Have Something Special to Offer?*, 16 HUMAN PSYCHOPHARMACOLOGY (SUPPLEMENT) S67, S67 (2001); Strong, *supra* note 6, at 466.

32. Strong, *supra* note 6, at 466.

33. See Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, STAN. TECH. L. REV. ¶11 (2007). The increase occurs according to  $2n-1$  pairs of enantiomers (where  $n$  is the number of stereogenic centers in a given molecule). *Id.*

34. History of HPLC, <http://kerouac.pharm.uky.edu/asrg/hplc/history.html> (last visited May 12, 2008).

35. Strong, *supra* note 6, at 466.

36. Chiral HPLC works by exploiting the differences observed in the stability of constituent enantiomers. Specifically, single enantiomers are immobilized. Then, the less stable of the two enantiomers elutes or flows out of the HPLC column before the more stable enantiomer. Once separated via the HPLC column, a detector then indicates the retention times of the individual enantiomers, and thus facilitates collection. Thus, the enantiomers are identifiable and separated. Using chiral HPLC, retention times are unique to a given enantiomer. See Mark Earll, *Online Guide to Chiral HPLC*, <http://www.raell.demon.co.uk/chem/CHIbook/chiral.htm> (last visited May 12, 2008).

37. *The USAN Perspective*, *supra* note 9 (noting that most pharmaceuticals were developed and marketed as a mixture of enantiomers prior to widespread use of chiral separation techniques such as HPLC).

38. See Caldwell, *supra* note 31, at S70 (noting that technological advances have facilitated the separation of enantiomers).

Writings and Discoveries.”<sup>39</sup> In 1790, the first Congress established that such exclusivity would be granted as a patent for a term of years to anyone who “[I]nvented or discovered any useful art, manufacture, engine, machine, or device, or any improvement therein not before known or used . . . [so long as the invention was] sufficiently useful and important . . . .”<sup>40</sup> Ultimately, a patent grants an inventor time-limited market exclusivity over his or her invention in exchange for making public the knowledge needed to make or practice his or her discovery.<sup>41</sup> With novelty, utility, and discovery (later termed “non-obviousness”) requirements limiting patentability, Congress sought to promote scientific progress by balancing the public’s interest in benefitting from the disclosure of ideas and the free exchange of information against incentivizing invention by the inventor reaping a financial reward for his or her efforts.<sup>42</sup> While Congress has modified the Patent Act from time to time to keep pace with changing ideas and technology, the three requirements of novelty, utility, and invention remain essentially intact.<sup>43</sup>

The history of the non-obviousness (or invention) requirement reflects the importance of the standard to courts.<sup>44</sup> Further, in 1793, Congress noted that “simply changing the form or the proportions of any machine, or composition of matter, in any degree, shall not be deemed a discovery.”<sup>45</sup> In the seminal 1850 case, *Hotchkiss v. Greenwood*, the Supreme Court held that a patent-worthy invention required more than “the work of the skilful mechanic.”<sup>46</sup> Subsequent courts followed with

39. U.S. CONST. art. I, § 8.

40. Act of Apr. 10, 1790, ch. 7, § 1, 1 Stat. 109, 109–10.

41. See *id.* § 2; 35 U.S.C. § 112 (2008).

42. *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150–51 (1989) (noting that “the federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years;” the bargain reflects Congress’ determination of the Patent Clause as maintaining the spirit of free competition and open exploitation of knowledge goods in the public domain already).

43. “Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” 35 U.S.C. § 101 (2006); 35 U.S.C. § 103 (2006) (providing that only non-obvious subject matter is patentable).

44. NONOBVIOUSNESS—THE ULTIMATE CONDITION OF PATENTABILITY: PAPERS COMPILED IN COMMEMORATION OF THE SILVER ANNIVERSARY OF 35 USC 103 (John F. Witherspoon ed. 1980), cited in ROBERT MERGES & JOHN DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 643 (3d ed. 2002) (explaining that nonobviousness was considered to be the “ultimate condition of patentability” by many patent lawyers).

45. Act of Feb. 21, 1793, 1 Cong. ch. 11, § 2, 1 Stat. 318. The words “sufficiently useful and important” were included in the 1790 Patent Act to qualify which inventions were worthy of a patent were not found in the 1793 Act.

46. *Hotchkiss v. Greenwood*, 52 U.S. 248, 267 (1851).



the requirement that an applicant demonstrate a “flash of creative genius” before a patent would be issued.<sup>47</sup>

Congress and the judiciary realized over time that the patent system needed to reflect the reality that scientific invention often occurs as a series of steps rather than a solitary instant of inspiration or genius. Reluctant to award patents for trivial improvements, however, Congress codified what became known as the “non-obvious requirement” in the 1952 Patent Act.<sup>48</sup> In its present form, the non-obvious requirement is codified at 35 U.S.C. § 103(a):

A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.<sup>49</sup>

Subsequently, the Court interpreted the language of Section 103(a) as requiring something of a qualitative advancement over previous inventions before extending an inventor the exclusivity that a patent confers.<sup>50</sup> The Court articulated this principle in *Graham v. John Deere Co.*:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.<sup>51</sup>

Pharmaceutical companies seeking patents for enantiomers developed through the resolution of racemic mixtures have found the non-obviousness requirement problematic.<sup>52</sup> Indeed, the United States Court

47. *Cuno Eng'g Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 91 (1941).

48. Patent Act of 1952, Pub. L. No. 593, ch. 950, § 103, 66 Stat. 798 (1952) (codified as amended at 35 U.S.C. § 103 (2006)).

49. 35 U.S.C. § 103(a) (2006).

50. *See Graham v. John Deere Co.*, 383 U.S. 1, 9 (1966).

51. *Id.* at 18.

52. *See In re Williams*, 171 F.2d 319, 320 (C.C.P.A. 1948) (noting that the patent examiner's contention that an enantiomer, having existed as part of the racemic mixture, cannot be novel was erroneous). Reversing the Board of Appeals' rejection of a purified enantiomer patent application, the court noted that the “existence of a compound as an ingredient of an-

of Customs and Patent Appeals (CCPA), the predecessor court to today's Federal Circuit, found applications for enantiomers developed through the resolution of racemic mixtures *prima facie* obvious.<sup>53</sup> The CCPA, however, allowed applicants to rebut the presumption of obviousness if the resulting enantiomer had unexpected properties.<sup>54</sup>

How unexpected or nonobvious an enantiomer's observed property must be when attempting to patent a resolved racemate is not altogether clear from the case law, however. For example, in *In re Adamson*, the CCPA upheld a United States Patent and Trademark Office (USPTO) rejection of a single-enantiomer having greater spasmolytic activity yet only slightly higher toxicity than either the racemic mixture or the corresponding enantiomer.<sup>55</sup> Particularly troubling for the CCPA was a reference in an organic chemistry text. The reference noted the method used by the applicant for resolving racemic mixtures generally and the principle that corresponding enantiomers may have different physiological properties specifically.<sup>56</sup> Apparently, the unexpected result observed when resolving the racemate did not reach a threshold nonobviousness requirement separate from the unexpected property observed.<sup>57</sup> Eighteen years later, however, in *In re May*, the CCPA reversed a USPTO rejection for a patent on an enantiomer resolved from a known racemic mixture. The court held that the enantiomer had surprising properties and was consequently nonobvious.<sup>58</sup> The CCPA also noted that, while the prior art

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other substance does not negative novelty in a claim to the pure compound, although it may, of course, render the claim unpatentable for lack of invention." *Id.* at 320.

53. See *In re Adamson*, 275 F.2d 952, 954-55 (C.C.P.A. 1960) (affirming a PTO patent application rejection because the prior art disclosed the racemate of the applicant's enantiomer, a method for reducing enantiomers from a racemic mixture, and the prediction that the toxicity of the racemate would lie somewhere between the two enantiomers).

The *Adamson* decision may be read as suggesting that obtaining a patent for an enantiomer resulting from resolving a racemate will become increasingly more difficult as technology advances. See Darrow, *supra* note 33, at ¶10.

54. See *In re May*, 574 F.2d 1082, 1090-94 (C.C.P.A. 1978) (finding that an isolated stereoisomer was nonobvious because the stereoisomer was unpredictably not addictive). The court invalidated claim 6 in the patent, which claimed the *hydrochloride* salt of a class of compounds, as anticipated by prior art that expressly disclosed the *hydrobromide* and noted that salts were previously described as being especially suitable for use. *Id.* at 1089-90.

55. *In re Adamson*, 275 F.2d at 952-53. That the enantiomer claimed a *laevo*-isomer of a compound selected from a class of thiophenol benzhexol or 1-cyclohexyl-1-phenyl-3-piperidinopropan-1-ol had only slightly higher toxicity is somewhat profound, clinically. Efficacious anti-cholinergic treatment of Parkinson's disease and toxicity are dependently related; the more toxic the dose, the more effective the regimen. See J.D. Parkes, *Comparative Trial of Benzhexol, Amantadine, and Levodopa in the Treatment of Parkinson's Disease*, 37 J. NEUROLOGY, NEUROSURGERY & PSYCHIATRY 422 (1974); Daniel J. DeNoon, *L-Dopa Doesn't Hasten Parkinson's Disease*, WEBMD, Dec. 7, 2004, <http://www.webmd.com/parkinsons-disease/news/20041208/l-dopa-doesnt-hasten-parkinsons-disease>.

56. *In re Adamson*, 275 F.2d at 953-54.

57. *Id.*

58. *In re May*, 574 F.2d at 1090-94.

contained the racemic mixture and although the mix had both analgesic and non-addictive properties, isolating a stereoisomer with both properties was unexpected.<sup>59</sup> Moreover, most previous efforts to develop a molecule with both analgesic and non-addictive properties had been unsuccessful.<sup>60</sup>

In contrast with the Federal Circuit's historically strict and arguably formulaic obviousness inquiry as applied to other fields,<sup>61</sup> the court's obviousness analysis as applied to pharmaceuticals tends to be highly nuanced.<sup>62</sup> In *KSR International Co. v. Teleflex Inc.*, the Supreme Court chastised the Federal Circuit for its inflexible application of this rule.<sup>63</sup> One scholar has suggested that the Federal Circuit's nuanced application of the (non)obviousness analysis for pharmaceutical patents already comports with the more flexible standard articulated by the Supreme Court in *KSR*.<sup>64</sup> Regardless, the Federal Circuit's approach provides little bright-line guidance to applicants seeking patents on single enantiomers developed from previously known racemic mixtures. In *Sanofi-Synthelabo v. Apotex, Inc.*, the Federal Circuit upheld the validity of a patent that claimed the bisulfate salt of a single enantiomer, finding that a prior art reference to the racemic free base did not render the claim obvious.<sup>65</sup> First, the court found that the unpredictable pharmaceutical properties of the single enantiomers rendered the patentee's choice to pursue the enantiomerically pure salt nonobvious.<sup>66</sup> Second, the court

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59. *Id.*

60. *Id.*

61. The Federal Circuit has historically applied a strict rule when evaluating the obviousness of patents from other fields, finding that unless an objective teaching, suggestion, or motivation to combine elements from the prior art prompted invention of the claimed specimen, the invention would be found non-obvious and thus patentable. See *In re Dembiczak*, 175 F.3d 994, 999–1001 (Fed. Cir. 1999) (noting that although several prior art references may have been combined to achieve the resulting claimed patented invention, no teaching, suggestion, or motivation in the prior art suggested the combination claimed specifically); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) (noting that teaching, suggestion, or motivation to combine elements of the prior art is an essential evidentiary aspect of an obviousness holding); *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998) (holding that combination of two prior art patents and a conference report does not result in an obviousness determination absent motivation to combine those references).

62. See Rebecca Eisenberg, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 377–79 (2008). The Federal Circuit follows a similar methodology as the CCPA for evaluating the obviousness of patents on molecules or compounds that are often developed by making small structural changes to existing chemicals in hope of finding a particular property. *Id.*

63. *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007) (rejecting the rigidity of teaching, suggestion or motivation test adopted by the Federal Circuit in favor of the more flexible approach adopted in *Graham*).

64. See Eisenberg, *supra* note 62, at 380.

65. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1378 (Fed. Cir. 2006).

66. *Id.* at 1378–79.

found that the extensive time and money that the patentee spent developing the racemate before redirecting efforts toward the enantiomer, and the unpredictability of salt formation, constituted additional indicators of nonobviousness.<sup>67</sup>

One year after *Sanofi-Synthelabo* and almost five months after *KSR*, the Federal Circuit decided two more cases involving patents on single-enantiomer drugs resulting from a previously-approved racemic drug resolution. Both cases involved infringement actions arising from a generic manufacturer's Abbreviated New Drug Application (ANDA) to the FDA. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, the challenger argued that Forest Laboratories' patent on the single-enantiomer drug was invalid for obviousness, noting that the racemate was in the prior art before Forest Laboratories developed the single-enantiomer.<sup>68</sup> The court rejected the generic challenger's argument, noting that resolution of the enantiomer had been quite difficult—many had failed despite the availability of HPLC.<sup>69</sup> Moreover, the court noted that while the prior art disclosed the racemate, one reference also suggested that the *other* enantiomer would be clinically significant—not the one developed by Forest Laboratories.<sup>70</sup> Thus, the court suggested Forest Laboratories' development of the enantiomer produced a surprising result in light of the prior art, which taught away from developing the enantiomer.

Meanwhile, in *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, the Federal Circuit decided in favor of the generic challenger, holding that the single-enantiomer patent was invalid as obvious.<sup>71</sup> Once again, the Federal Circuit noted that the prior art disclosed the racemate for the enantiomer at issue. Unlike in *Forest Labs*, where the prior art taught away from the patent claimed, the prior art in *Aventis* suggested that the enantiomer developed would be the clinically significant enantiomer.<sup>72</sup> Although the newly developed enantiomer displayed 18 times the potency as the other isomer from the racemate, the court did not consider this elevated potency a surprising result.<sup>73</sup> Much like the decision in *In re Adamson*, where increased potency was expected and thus inadequate to overcome obviousness,<sup>74</sup> the court noted:

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67. *Id.* at 1379.

68. *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

69. *Id.* at 1269.

70. *Id.* at 1268.

71. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1295 (Fed. Cir. 2007).

72. *Id.* at 1302.

73. *Id.*

74. *In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960).

[O]ne expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art. If it is known how to perform such an isolation, doing so "is likely the product not of innovation but of ordinary skill and common sense."<sup>75</sup>

Arguably consistent with *KSR*, the Federal Circuit's enantiomer jurisprudence is difficult to reconcile with a single, rigid standard. However, some common themes may be observed throughout the cases. The court will find an enantiomer developed from a racemate present in the prior art prima facie obvious.<sup>76</sup> Moreover, when the resolution process for an enantiomer exists in the prior art, overcoming the obviousness finding will be particularly difficult.<sup>77</sup> Nonetheless, the court may allow one or more factors to overcome this finding of obviousness. These factors include (1) observation of a surprising property or an unexpected combination of properties, including a property observed when the prior art teaches away from the result observed; and (2) an unusually difficult process of purifying the racemic mixture, particularly if others have failed. The Federal Circuit seemingly approaches racemate resolution as a fact-specific inquiry. Moreover, the court seems sensitive to the position in which a patent applicant finds herself when litigation commences. For example, the court seems less likely to invalidate a single-enantiomer patent if the patent has already issued and is challenged by a third-party, as in *Forest Labs* and *Sanofi-Synthelabo*.<sup>78</sup> However, the court gives less deference to a single-enantiomer patent that is being appealed from a rejection by the U.S. Patent and Trademark Office.<sup>79</sup> In other words, the Federal Circuit seemingly favors the presumption of patent validity following patent issuance from the U.S. PTO when confronted with a challenge to a single-enantiomer resulting from a resolved racemate.<sup>80</sup> While the court's enantiomer jurisprudence offers some guiding principles for pharmaceutical companies looking to engage in a chiral switch, the court has offered few bright line rules concerning the

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75. *Aventis*, 499 F.3d at 1302 (quoting *KSR Int'l Co. v Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

76. *See In re Adamson*, 275 F.2d at 952.

77. *See Aventis*, 499 F.3d at 1293.

78. *Forest Labs. v. Ivax Pharm., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007); *Sanofi-Synthelabo, Inc. v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006). *Cf. Aventis*, 499 F.3d at 1293.

79. *See In re Adamson*, 275 F.2d at 954. *Cf. In re May*, 574 F.2d 1082 (C.C.P.A. 1978).

80. 35 U.S.C. § 282 (2006) (noting that "a patent shall be presumed valid," and "the burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity:").

patentability of a single-enantiomer developed from a parent racemate. The result is a minefield of uncertainty awaiting patent applicants. As such, it is not surprising that Congress recently revisited the question of exclusivity for chiral switches.<sup>81</sup>

#### IV. FDA GRANTS EXCLUSIVITY TO CHIRAL SWITCHES, SECTION 505(u)

With the passage of the FDAAA, five years of market exclusivity became available to pharmaceutical companies bringing a single-enantiomer resulting from a racemic mixture to market. Section 505(u) states: "for . . . a single enantiomer that is contained in a racemic drug approved in another application . . . the applicant may . . . elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug."<sup>82</sup> In essence, the amendment provides the same market exclusivity to a chiral switch as is enjoyed by drugs conferred new chemical entity status. New chemical entities, and single-enantiomer drugs resulting from chiral switches by extension, are entitled to five years of market exclusivity.<sup>83</sup> However, approval under Section 505(u) is limited to two circumstances: (1) when the FDA requires new clinical investigations excluding bioavailability studies; and (2) when the applicant seeks approval for an indication in a different therapeutic class from that of the parent racemic drug.<sup>84</sup> Moreover, the applicant may not rely on studies conducted for the racemic drug when seeking market approval for the single-enantiomer, and the clinical studies provided must be conducted or sponsored by the applicant.<sup>85</sup> Prior to FDAAA enactment, pharmaceutical companies bringing a chiral switch to market could anticipate three years of market exclusivity at best.<sup>86</sup>

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81. See Senator Orrin Hatch, Floor Speech: The Food and Drug Administration Revitalization Act (May 1, 2007), available at [http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Print&PressRelease\\_id=1800&suppresslayouts=true](http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Print&PressRelease_id=1800&suppresslayouts=true).

82. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1113, 121 Stat. 823 (2007) (codified at 21 U.S.C. § 355(u)).

83. *Id.*

84. *Id.*

85. *Id.*

86. Strong *supra* note 6, at 475, 480 (noting that "the posture (of the FDA) was that single enantiomers of previously approved racemates contain a previously approved active moiety and are not new chemical entities, thus they are barred from five years of market exclusivity"). Single enantiomers would be eligible for three years of exclusivity but only where additional clinical investigations were performed. *Id.*

## CONCLUSION

While some may argue that the FDA is adding yet another avenue for lengthening exclusivity to drug companies who already use every possible tactic to extend the life of their product's exclusivity to the detriment of both generic drug companies and those expected to pay for the exclusivity enjoyed by these companies,<sup>87</sup> the reality is that the five years of exclusivity offered by the FDA is likely a time-limited phenomenon. With improved technology available to resolve racemates, drug companies are simply not pursuing development of racemic drugs at an appreciable rate anymore. For example, "the market share of single-enantiomer drugs increased from 27 percent in 1996 to 39 percent in 2002."<sup>88</sup> By 1998, sixty-nine percent of drugs in the latter stages of development or that had been newly licensed were single-enantiomer drugs.<sup>89</sup> Moreover, sales for single-enantiomer drugs increased by sixteen percent, equaling \$115 billion, from 1998 to 1999.<sup>90</sup>

Despite earnings of up to one million dollars per day,<sup>91</sup> the risks associated with developing a racemic drug make developing the mixed drug unlikely. For example, five years of exclusivity is probably not a large enough carrot for companies to deliberately develop a racemate and resolve the racemate following patent expiration. Many single-enantiomer drugs may have an increased safety profile, compared to racemic drugs, as unwanted side-effects can be caused, or worsened, by the opposite stereoisomer.<sup>92</sup> Therefore, companies are more likely to pursue development of the drug form most likely to survive FDA approval rather than a racemic drug that may look promising but ultimately falls short of FDA approval. Targeted drug development favors the development of single-enantiomer drugs as well.<sup>93</sup> For example, the development of designer drugs occurs begins with the elucidation of the receptor of interest's structure. Knowing the target receptor structure in detail enables development of the appropriate, corresponding enantiomer drug from the outset.<sup>94</sup> As suggested earlier, the trend of preferentially devel-

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87. If a drug is approved by the FDA while under patent, the sponsor is able to recoup the time elapsed during the drug-approval process. 35 U.S.C. § 156 (2006).

88. *The USAN Perspective*, *supra* note 9. In 1983, three percent of newly-licensed drugs were single enantiomer drugs, whereas in 1991, this figure increased to twenty-one percent. Caldwell, *supra* note 31, at S69.

89. Caldwell, *supra* note 31, at S69.

90. De Palma, *supra* note 12.

91. Pascal, *supra* note 29, at 547.

92. See generally Handley, *supra* note 16 (providing specific examples where opposite stereoisomers have caused or worsened unwanted side-effects).

93. Caldwell, *supra* note 31.

94. *Id.*

oping single-enantiomer drugs as opposed to racemic drugs is reflected in the market as well.<sup>95</sup>

Some might be concerned that FDAAA Section 505(u) includes a benefit to drug developers that was not previously available and may not be currently available via the patent system and that this benefit was not balanced with some gain for generic companies or the public. However, the effect of any benefit resulting from Section 505(u) is likely short-lived; drug developers are developing single enantiomer drugs in the first instance because developing single enantiomer drugs has been rendered almost routine by technology and because the safety profile for an as yet unapproved drug is enhanced when the drug is a single enantiomer and not a racemic mixture.<sup>96</sup> Thus, any life cycle management gain realized by an extended term of exclusivity offered under Section 505(u) is likely offset by the rigor of the FDA's new drug approval process. A safer drug is more likely to survive clinical trials and enjoy FDA market approval than a less safe, artificially developed drug, as in the case of a racemic mixture. Consequently, any concerns one may have about Section 505(u) should be tempered by the realities the drug approval brings to life cycle considerations. In the end, Section 505(u)'s impact on drug exclusivity will be short-lived.

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95. *The USAN Perspective*, *supra* note 9; *see also infra* Part II.

96. *See Hatch*, *supra* note 81.