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REBUTTING OBVIOUSNESS IN THE PHARMACEUTICAL INDUSTRY: SECONDARY CONSIDERATIONS OF ANALOGS

Jolie D. Lechner*

Abstract

Pharmaceutical companies depend on patent protection to recuperate the high costs of research and development. In regards to the patentability of structurally related compounds, the courts must decide whether a compound is obvious in view of its structurally similar prior art. In general, a compound is non-obvious over the structurally related prior art if the compound exhibits unexpected results. However, placing primary emphasis on a compound's unexpected properties is out of step with the realities of drug development. For example, during drug development, chemists will modify a compound's structure until they produce a compound that exhibits optimal pharmakinetic properties. This iterative process relies on the perseverance of scientists to pave the road to drug discovery—not unexpected results.

This Note advocates for the elevation of the failure of others to make a drug that benefits society and the long-felt but unmet need for that treatment in the obviousness inquiry. These factors highlight the underappreciated realities of the drug discovery process, the immense effort that precedes a drug's delivery to market, and the profound effect pharmaceuticals can have on disease treatment. In giving greater credence to the failure of others to develop a drug and the unmet need for that treatment, courts can resolve the current disconnect between the laboratory and patent law. By rewarding innovators that embark on a logical research plan that ends in the development of a beneficial drug, patent law will encourage companies to invest in drug development and produce drugs that benefit society.

INTRODUCTION

"[P]atents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation.'"[1] This was illustrated early on in *The Incandescent Lamp Patent* case.[2] In that case, the Supreme Court invalidated a patent for an incandescent lamp that used a conductor composed of "fibrous or textile material."[3] While the Court reasoned that the specification was "too

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[1] Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 997 (Fed. Cir. 2009) (quoting *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)).

[2] The Incandescent Lamp Patent, 159 U.S. 465 (1895).

[3] *Id.* at 471.

indefinite . . . [for a] valid monopoly," the Court's decision was grounded in economics.[4] Simply put, the plaintiffs' lamp "was never a commercial success" due to the "defective" lamp chamber.[5] It was Thomas Edison, the alleged infringer, who produced a domestic lamp fit for the marketplace. While Edison's design certainly had precedents in earlier, ineffective incandescent lamp designs, his ceaseless efforts to perfect the device resulted in a working product. Only after extensive experimentation with conductor thickness, "thirty or forty different woods of exogenous growth," and various types of bamboo from China and Japan did Edison develop a useful light bulb.[6] This invention met society's long-felt but unmet need for artificial light at night. As a result, the Court refused to allow the plaintiffs' "imperfectly successful experiments" to stand in the way of Edison's "brilliant discover[y]."[7]

The issues underlying the Supreme Court's decision are still relevant in patent law today. While the statutory definition of non-obviousness[8] did not exist at the time of *The Incandescent Lamp Patent*, the Court placed emphasis on factors like the failure of the other inventors to create a working lamp and the public's long-felt need for artificial light.[9] Today, courts look to these factors, called secondary considerations, as evidence of non-obviousness, which is a requirement for patentability.[10]

In the pharmaceutical industry, evaluating the non-obviousness of new chemical compounds requires a nuanced analysis.[11] Drug development is "profoundly affected" by structurally related compounds like enantiomers, isomers, and analogs.[12] Thus, the statutory hurdle of non-obviousness[13] plays an increasingly important role in the patentability of such compounds. The Federal Circuit has maintained that "structural similarity between claimed and prior art subject matter, proved by combining references

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[4] *Id.* at 477.
[5] *Id.* at 471.
[6] *Id.* at 473-74.
[7] *Id.* at 474.
[8] In 1952 Congress codified the non-obviousness requirement of patentability in 35 U.S.C. §103; for commentary regarding the enactment of 35 U.S.C. §103 see CRAIG A. NARD, THE LAW OF PATENTS 321-26 (2008).
[9] The Incandescent Lamp Patent, 159 U.S. at 471-77.
[10] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (reaffirming Graham v. John Deere Co.).
[11] While structurally similar compounds can appear deceptively obvious, making small changes in a compound's structure can result in molecules with vastly different biological and pharmacological properties. As a result, structurally related compounds have presented the courts with a complex obviousness analysis that has evolved into a distinct area of patent law. *See* Rebecca M. Wilson & Samuel J. Danishefsky, *Small Molecule Natural Products in the Discovery of Therapeutic Agents: The Synthesis Connection*, 71 J. ORG. CHEM. 8329, 8336 (2006) ("Even with all of the advances, ours is a fickle science of limited predictive capacity. The fact that so much success has been accomplished should not obscure the fact that there is so much that we do not know how to do at all, or can do only poorly."); *In re* Jones, 958 F.2d 347, 349 (Fed. Cir. 1992) (noting that "[t]he question of 'structural similarity' in chemical patent cases has generated a body of patent law unto itself").
[12] For a minireview regarding the challenge presented by the structurally related compounds atropisomers see Jonathan Clayden et al., *The Challenge of Atropisomerism in Drug Discovery*, 48 ANGEW. CHEM. INT. ED. 6398, 6398 (2009).
[13] 35 U.S.C. §103.

or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness."[14] In other words, a lead compound's structure can provide motivation for further structural modifications resulting in new, but obvious compounds.[15] For example, the Federal Circuit in *In re Dillon* considered the obviousness of tetra-orthoesters with respect to tri-orthoesters in the area of fuel chemistry.[16] While both classes of compounds function as fuel additives, tetra-orthoesters reduce the emission of solid particulates during combustion whereas tri-orthoesters prevent phase separation between fuel and alcohol co-solvents.[17] Despite this difference, due to the structural similarity between tetra- and tri-orthoesters and their similar applications as fuel additives, the Federal Circuit reaffirmed that the applicant's tetra-orthoesters were prima facie obvious.[18] Furthermore, the court noted that the applicant "had the opportunity to rebut the *prima facie* case," but failed to demonstrate that the tetra-orthoesters possessed "unexpectedly improved properties" over the prior art.[19]

As illustrated by *In re Dillon*, courts have tuned the obviousness analysis in chemical patent cases to center on unpredictable results. Thus, a patentee can rebut the prima facie case of obviousness based on structural similarity if the claimed compound "possess[es] unexpectedly improved properties" over the prior art.[20] To date, case law has "recogniz[ed] the vital role" of unexpected results in defeating obviousness allegations in the context of structural similarity.[21] For example, consider the obviousness of Type 2 diabetes drug pioglitazone, which belongs to a known class of compounds called thiazolidinediones ("TZDs").[22] While pioglitazone has a close structural relationship to a prior art compound with antidiabetic activity, the Federal Circuit held that the compound's "unexpectedly superior properties" rendered the molecule non-obvious.[23] Likewise, in *Proctor & Gamble Co. v. Teva Pharmaceuticals*, the Federal Circuit reaffirmed that risedronate, the active ingredient of P&G's osteoporosis drug Actonel®,

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[14] Takeda Chem. Indus. v. Alphapharm. Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)); *see also* Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness."); *In re* Payne, 606 F.2d 303, 314-15 (C.C.P.A. 1979) (noting "the presumption of obviousness based on close structural similarity"); *see generally* Helmuth A. Wegner, *Prima Facie Obviousness of Chemical Compounds*, 6 APLA Q. J. 271 (1978) (discussing prima facie obviousness of structurally related compounds such as homologs, isomers, stereoisomers, etc.).

[15] Takeda Chem. Indus., Ltd., 492 F.3d at 1356 (quoting *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

[16] *In re* Dillon, 919 F.2d 688, 690-91 (Fed. Cir. 1990) (en banc).

[17] *Id.* at 690.

[18] *Id.* at 692.

[19] *Id.* at 692-93.

[20] *Id.* at 692-93.

[21] Takeda Chem. Indus., 492 F.3d 1350, 1364 (Dyk, J., concurring); *see also* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1371 (Fed. Cir. 2007) (finding a species claim obvious because Pfizer "simply failed to prove that the results [were] unexpected"); Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1010 (Fed. Cir. 2009) (reaffirming the district court's finding that "the purportedly unexpected property of pantoprazole is in fact an expected property . . . . [showing] a sufficient case of obviousness to defer the matter for trial on the merits").

[22] Takeda Chem. Indus., 492 F.3d at 1352-53.

[23] *Id.* at 1361-62.

was non-obvious due to unexpected properties.[24] In reaching its decision, the Federal Circuit placed emphasis on a researcher's testimony that she was "very surprised" at risedronate's efficacy and a doctor's statement that "the superior properties of risedronate were unexpected and could not have been predicted."[25]

The reasoning underlying the relationship between patentability and unpredictable results is understandable: how could an invention be obvious if its properties catch the inventor off-guard? But this test is often at odds with the reality of how drug development is performed.[26] For example, in small molecule R & D, chemists will make minor modifications to a lead compound's structure with the goal of optimizing its efficacy and safety.[27] The compounds that show promising activity are subjected to animal studies as well as human testing during three consecutive phases of clinical trials.[28] During this long and expensive process, many compounds are abandoned along the way due to insufficient efficacy and safety concerns.[29] All the while, chemists continue to modify the lead structure until optimal pharmakinetic properties are achieved.[30] This methodical process relies on the perseverance of scientists to pave the road to drug discovery—not on unpredictable results.[31]

The disconnect between laboratory methods and the courtroom's standards for obviousness threatens to stifle the development of innovative drugs. Pharmaceutical science is a risky business that relies on patent protection to fuel costly research and development.[32] For example, developing a new drug fit for the marketplace can take

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[24] Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 997.

[25] *Id.*

[26] *See* Kristen C. Buteau, *Deuterated Drugs: Unexpectedly Nonobvious?*, 10 J. HIGH TECH. L. 22, 23 (2009) (commenting that "pharmaceutical patents are especially susceptible to an obviousness challenge because the natural progression of science necessarily builds upon past discoveries and requires considerable experimentation through trial and error, thereby potentially rendering the invention obvious-to-try").

[27] *See generally* RICHARD B. SILVERMAN, THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION, 17-61 (2d ed. 2004).

[28] For a description of clinical trials during drug development *see* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 JOURNAL OF HEALTH ECONOMICS 151, 155-56 (2003).

[29] YALI FRIEDMAN, BUILDING BIOTECHNOLOGY: BUSINESS, REGULATIONS, PATENTS, LAW, POLITICS, SCIENCE 45-46 (3d ed. 2008) (commenting that "[t]he Tufts Center for the Study of Drug Development found that only five in five thousand small-molecule compounds that enter pre-clinical testing make it to human testing. Of these five, only one is approved").

[30] SILVERMAN, *supra* note 27, at 17-18; Expert Report of John G. Gleason, Ph.D. on Patent Validity at 4, Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., No. 07-1596 (GEB)(JJH), 2009 WL 3153316 (D.N.J. Aug. 19, 2009).

[31] SILVERMAN, *supra* note 27, at 17 (noting that, "rational approaches [in drug development] are directed at lead discovery. It is not possible, with much accuracy, to foretell toxicity and side effects, anticipate transport characteristic, or predict the metabolic fate of a drug. Once a lead is identified, its structure can be modified until an effective drug is prepared").

[32] Michael Enzo Furrow, *Analyzing the Laws, Regulations, and Policies Affecting FDA-Regulated Products: Pharmaceutical Patent Life-Cycle Management After KSR v. Teleflex*, 63 FOOD & DRUG L.J. 275, 278 (2008); *see also* Biotechnology Indus. Org. v. District of Columbia, 496 F.3d 1362, 1372 (Fed. Cir. 2007) ("We have long acknowledged the importance of the patent system in encouraging innovation. Indeed, 'the encouragement of investment-based risk is the fundamental purpose of the patent grant, and is based directly on the right to exclude.' . . . Importantly, the patent system provides incentive to the

innovator drug firms ten to fifteen years[33] and cost $1.5 billion per drug.[34] With little more than the hope of unpredictable results to rely on in obtaining much-needed patent rights, pharmaceutical companies will not invest in the lengthy and uncertain process of drug discovery.[35] Considering that "pharmaceutical products increase longevity, improve the quality of life, and often result in medical cost savings,"[36] courts should rely on objective indicia of non-obviousness that do not "penalize[] people in areas of endeavor where advances are won only by great effort and expense."[37]

Giving greater credence to additional considerations, such as the failure of others to develop a drug that fulfills society's long-felt need for disease treatment, will encourage companies to develop drugs that benefit society.[38] Unlike the unpredictable results analysis, these factors (1) reward innovators that have the skill to execute a bright idea; and (2) encourage companies to pursue difficult projects whose completion can greatly benefit society. In other words, a company could give their support to a "researcher [who] dared to follow a logical plan"[39] with some confidence that their support would be rewarded.

The introduction of this Note introduces the real-world significance of others' failures to meet a long-felt but unmet societal need in advancing technology. Part I provides background into the patent system and the obviousness of structurally related compounds. Part II uses two recent pharmaceutical patent cases, *Eli Lilly & Co. v. Sicor Pharmaceuticals, Inc.*[40] and *Merck Sharp & Dohme Pharmaceuticals, SRL v. Teva Pharmaceuticals USA, Inc.*,[41] to illustrate the paramount role of (1) others' unsuccessful efforts; and (2) the societal benefits of the drugs that meet a long-felt need in establishing non-obviousness. Part III proposes that courts should place primary emphasis on the failure of others and long-felt need in the obviousness analysis of structurally related

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innovative drug companies to continue costly development efforts.") (quoting Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383 (Fed. Cir. 2006)).

[33] Furrow, *supra* note 32, at 278.

[34] *Id.* at 283.

[35] *See* Carmelo Giaccotto et al., *Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry*, 48 J. LAW & ECON. 195, 211 (2005) (commenting that scholars have argued that "the most innovative drugs are riskier and costlier to produce but presumably have the greatest social benefits").

[36] *Id.* at 195.

[37] *In re* Merck & Co., 800 F.2d 1091, 1100 (Baldwin, J., dissenting) (arguing that the obvious-to-try test should not be applied to research areas that are high cost and labor-intensive, e.g., pharmaceuticals).

[38] *See* Joseph P. Meara, Note, *Just Who is the Person Having Ordinary Skill in the Art? Patent Law's Mysterious Personage*, 77 WASH. L. REV. 267, 295-96 (2002) ("Long-felt need and failure of others to make the invention should not be utilized as 'secondary' considerations, but rather as objective evidence of actual skill in the art . . . When a problem is old in the art and has been the subject of more than de minimus research, it suggests that no one of any skill level was able to solve it. When combined with actual evidence that others failed to solve the problem, one can infer that the solution has eluded those of ordinary skill.").

[39] *In re* Merck & Co., 800 F.2d at 1100 (Baldwin, J., dissenting) (arguing that the obvious-to-try analysis is inapplicable to the pharmaceutical field because the test would render any effective drug obvious simply because it followed from "a logical research plan").

[40] Eli Lilly & Co. v. Sicor Pharm., Inc., 705 F. Supp. 2d 971 (S.D. Ind. 2010).

[41] Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., No. 07-1596 (GEB)(DEA), 2009 WL 3153316 (D.N.J. Aug. 19, 2009).

compounds like analogs. Finally, this Article concludes that the patent system's recognition of others' unsuccessful efforts to satisfy a long-felt need is necessary to encourage drug development.

I. BACKGROUND: REQUIREMENTS FOR PATENTABILITY

A. The Patent System

Patent law is grounded in incentives.[42] The United States Patent and Trademark Office ("PTO") induces inventors to disclose their discovery to the public by offering a financial reward.[43] To obtain a patent, the inventor must disclose subject matter that is novel,[44] useful,[45] and non-obvious.[46] Patent law's novelty requirement bars a patent for an invention that is not new.[47] For example, an invention is not novel if "it was made before; it was sold more than a year before a patent application was filed; or it was otherwise subject to prior use or knowledge."[48] In addition to being novel, patent-worthy inventions must be useful.[49] This requirement is easily met, as an invention need only work under experimental conditions.[50]

The "final gatekeeper of the patent system" is the non-obviousness requirement.[51] Obviousness is regarded as the "ultimate condition of patentability"[52] because it evaluates the technical merits of an invention.[53] This statutory prerequisite considers "whether an invention is a big enough technical advance" to warrant patent protection.[54] While non-obviousness is "the most important requirement"[55] for patentability, it has catalyzed "controversy"[56] regarding the patentability of structurally similar compounds.[57]

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[42] Giles S. Rich, *The Vague Concept of "Invention" as Replaced by § 103 of the 1952 Patent Act*, 14 FED. CIR. B.J. 147 (2004); *but see* David Conforto, *Traditional and Modern-Day Biopiracy: Redefining the Biopiracy Debate*, 19 J. ENVTL. L. & LITIG. 358, 367-68 (2004) (arguing that patent law disincentives scientific breakthroughs because patent rights are awarded to a "MegaPharm" company rather than the "innovator who actually makes the discovery"); Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 HIGH TECH. L.J. 1, 5 (1992) (noting that "it is safe to say there is a consensus among economists that in the aggregate patents offer only a very limited incentive to invent").
[43] NARD, *supra* note 8, at 2.
[44] 35 U.S.C. § 102.
[45] 35 U.S.C. § 101.
[46] 35 U.S.C. § 103.
[47] 35 U.S.C. § 102; *see also* NARD, *supra* note 8, at 187-88.
[48] Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CAL. L. REV. 803, 811 (1988).
[49] 35 U.S.C. § 101.
[50] Merges, *supra* note 48, at 812.
[51] *Id.*
[52] NONOBVIOUSNESS: THE ULTIMATE CONDITION OF PATENTABILITY (John F. Witherspoon ed., 1980).
[53] Merges, *supra* note 48, at 812.
[54] *Id.*
[55] *Id.*
[56] *See* Donald R. Dunner & Ronald P. Kananen, *Nonobviousness and the Court of Customs and Patent Appeals—Twenty-Five Years in Review*, in NONOBVIOUSNESS, *supra* note 52, at 3:114 (commenting "that Section 103 is, despite its seeming clarity, a generator of controversy").
[57] *In re* Jones, 958 F.2d 347, 349 (Fed. Cir. 1992) ("The question of 'structural similarity' in chemical patent cases has generated a body of patent law unto itself.") (citing Helmuth A. Wegner, *supra* note 14).

B. Determining Obviousness

In *Graham v. John Deere Co.*, the Supreme Court outlined the test for determining obviousness.[58] The Court determined that "[u]nder [35 U.S.C.] § 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."[59] Notably, the Supreme Court authorized courts to also use secondary considerations such as commercial success, the failure of others, long-felt but unmet needs,[60] and unexpected results in evaluating obviousness.[61]

Secondary considerations,[62] also called objective considerations, consider "evidence outside the intrinsic features of the invention and focus on the real-world circumstances surrounding [an invention's] origin and commercialization."[63] When there is a nexus between such considerations and the merits of the claimed invention,[64] secondary considerations "alone may defeat a claim of obviousness."[65] Moreover, such objective considerations "may often be the most probative and cogent evidence in the record."[66] Thus, secondary considerations are not just "icing on the cake,"[67] but "must be considered before the conclusion on obviousness is reached."[68] For example, in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals*,[69] the District Court for the Southern District of Indiana opined that even though the defendants "failed to establish a prima facie case of structural obviousness [of the drug olanzapine] . . . . the court is required to examine the objective evidence of nonobviousness in the record."[70] Thus, only after the court evaluated: (1) the long-felt need for a better antipsychotic drug like olanzapine; (2) the failure of others to develop a safe antipsychotic drug; (3) olanzapine's commercial

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[58] Graham v. John Deere Co., 383 U.S. 1, 17*;* KSR Int'l Co. v. Teleflex Inc. 550 U.S. 398, 406 (reaffirming Graham v. John Deere Co.).
[59] Graham v. John Deere Co., 383 U.S. at 17.
[60] *Id.* at 17-18; *see* Merges, *supra* note 48, at 816-19 for commentary regarding the origins of secondary considerations.
[61] U.S. v. Adams, 383 U.S. 39, 51-52 (1966); KSR Int'l Co. v. Teleflex Inc., 550 U.S. at 416.
[62] Honorable Giles Rich commented that he did "not believe the Supreme Court intended to signify anything by the term 'secondary'. . . . [and that secondary considerations should] be looked upon for what they factually are, *circumstantial evidence of unobviousness of the highest probative value*[.]" Giles S. Rich*, Laying the Ghost of the "Invention" Requirement*, *in* NONOBVIOUSNESS, *supra* note 52, at 1:513.
[63] Merges, *supra* note 48, at 816.
[64] Ruiz v. A.B. Chance Co., 234 F.3d 654, 668 (Fed. Cir. 2000) (citing Simmons Fastener Corp. v. Ill. Tool Works, Inc., 739 F.2d 1573, 1575 (Fed. Cir. 1984)).
[65] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 (N.D.W. Va. 2004), *aff'd* 161 Fed. Appx. 944 (Fed. Cir. 2005)).
[66] Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).
[67] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).
[68] Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., 2009 WL 3153316, at *50 (quoting Hybritech Inc., 802 F.2d at 1380).
[69] Zenith Goldline Pharmaceuticals is now known as Ivax Pharmaceuticals, Inc. *See* Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1373 (Fed. Cir. 2006).
[70] Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 364 F. Supp. 2d 820, 905-06 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

success; (4) the drug's industry acclaim; and (5) the compound's unexpected results, did the court conclude olanzapine was unobvious.[71]

II. REBUTTING THE OBVIOUSNESS OF ANALOGS

A. Introduction to Drug Discovery and Analogs

Most drugs are classified as structurally specific, meaning that they act at specific sites like a receptor or enzyme.[72] So, the activity and potency of structurally specific drugs are "very susceptible to small changes in chemical structure."[73] During drug discovery, chemists will modify a lead compound to generate structurally related compounds, called analogs.[74] This iterative process allows researchers to determine how a compound's biological activity is affected by structural modifications.[75] After enough analogs are prepared and studied, researchers can make conclusions regarding structure-activity relationships.[76] Chemists will continue to make changes to a lead compound's structure until its pharmakinetic properties[77] are optimized and its toxicity is minimized.[78]

To illustrate the role of analogs in drug development, consider the compounds in Figure 1. Modifying the structure of lead compound A (called sulfanilamide when R = H) resulted in analogs possessing diuretic, antidiabetic, and antimicrobial properties.[79] In order to understand the relationship between the compound's structure and its biological effects, over 10,000 compounds resembling compound A were synthesized and subjected to biological testing.[80] The results demonstrated that the skeletal framework present in all compounds (shown in blue) was responsible, in part, for the observed biological activity.[81] However, analogs with different functional groups at the 4 position often resulted in decreased potency.[82] Thus, structure-activity-relationship studies, such as the development of compounds B-D, allow scientists to modify the lead compound's structure to optimize its pharmakinetic properties.[83]

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[71] *Id.* at 906-09.
[72] SILVERMAN, *supra* note 27, at 21-22.
[73] *Id.* at 21.
[74] Expert Report of John G. Gleason, Ph.D. on Patent Validity at 4, Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., No. 07-1596 (GEB)(JJH), 2009 WL 3153316 (D.N.J. Aug. 19, 2009); for a definition of analog see TRUDY MCKEE & JAMES R. MCKEE, BIOCHEMISTRY: AN INTRODUCTION 388 (Kent A. Peterson et al. eds., 2d ed. 1999).
[75] SILVERMAN, *supra* note 27, at 21-22.
[76] *Id.* at 22.
[77] Pharmacokinetic properties refer to a compound's absorption, distribution, and metabolism in the body, *see* Gleason, *supra* note 74, at 4.
[78] *Id.*
[79] SILVERMAN, *supra* note 27, at 10, 22.
[80] *Id.* at 22.
[81] *Id.*
[82] *Id.*
[83] *Id.*; *see also* Gleason, *supra* note 74, at 4.

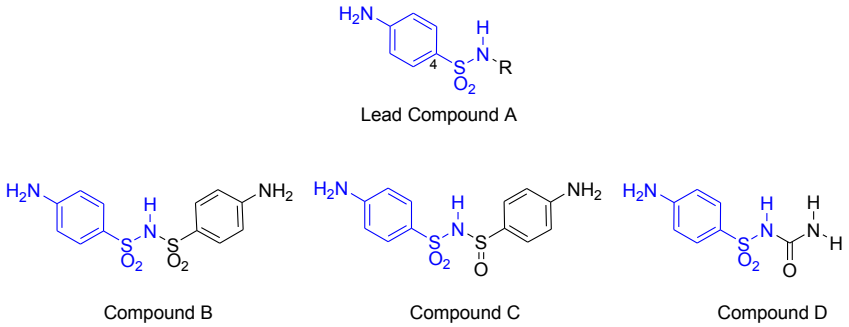

Figure 1: Analogs of sulfanilamide

B *The Failure of Others and Long-felt but Unmet Needs*

Advancing science is hard work. Even serendipitous discoveries are grounded in the daily grind of research. As discussed earlier, Thomas Edison was not immediately successful in his efforts towards a durable incandescent lamp conductor.[84] Only after extensive experimentation with nearly forty types of bamboo, which he acquired after dispatching a messenger to China and Japan, did Edison bring the domestic lamp into existence.[85] In so doing, Edison was the first of "a large number of persons, in various countries" to realize this goal.[86] Stated differently, Edison's success amidst the failure of others highlighted the technical merit of his invention.

Just as a chemist will attach different functional groups to a lead compound, Edison substituted bamboo for other conductors in an existing lamp design. Though the argument could be made that Edison's development was obvious, it ended in a product that met society's desire for artificial light.[87] To this end, an invention that improves the quality of life by satisfying a societal need should be rewarded. Although "long-felt need does not prove that the race actually occurred or that the patentee won it,"[88] it does set the parameters of competition by defining a goal. Furthermore, as shown in *Eli Lilly & Co. v. Sicor Pharmaceuticals, Inc.*[89] and *Merck Sharp & Dohme Pharmaceuticals, SRL v. Teva Pharmaceuticals USA, Inc.*,[90] patent law rewards inventors who enrich the public domain by achieving such goals, even in the face of allegations of obviousness.

i. Eli Lilly & Co. v. Sicor Pharmaceuticals, Inc.

1. Background of Nucleoside Analogs and Gemcitabine

[84] The Incandescent Lamp Patent, 159 U.S. 465, 473-74 (1895).
[85] *Id.* at 474.
[86] *Id.* at 471.
[87] *See* Tom Arnold, *Future Considerations—Views of a Private Practitioner*, in NONOBVIOUSNESS, *supra* note 52, at 8:5 (commenting that "many of our most worthwhile inventions, including Edison's electric light patent . . . . would have been obvious to all [based upon prior art]").
[88] Merges, *supra* note 48, at 872.
[89] Eli Lilly & Co. v. Sicor Pharm., Inc., 705 F. Supp. 2d 971 (S.D. Ind. 2010).
[90] Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., 2009 WL 3153316 (D.N.J., Aug. 19, 2009).

The case of *Eli Lilly & Co. v. Sicor Pharmaceuticals, Inc.*[91] concerns the patentability of gemcitabine, which is sold for the treatment of ovarian, breast, lung, and pancreatic cancer by Eli Lilly under the trade name Gemzar® (Figure 2).[92] Nucleoside analogs, like gemcitabine, are structurally related to naturally occurring nucleosides, which are the building blocks of DNA.[93] As shown in Figure 2, nucleosides consist of a five-carbon sugar ring attached to a base.[94] To avoid confusion when identifying atoms in the base and sugar components, a superscript prime is used to label the atoms of the sugar ring.[95]

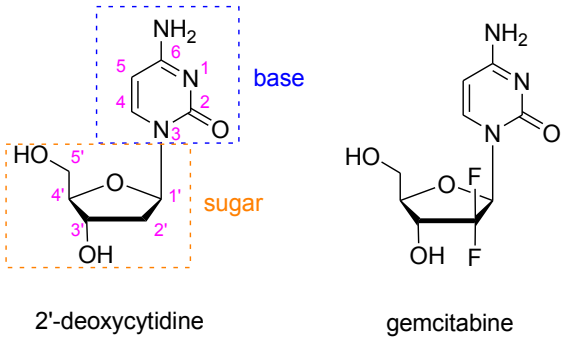

Figure 2: The naturally occurring nucleoside 2'-deoxycytidine and nucleoside analog gemcitabine

"The chemical modification of nucleosides . . . [is] a major research topic in bioorganic and medicinal chemistry."[96] Investigations into this class of compounds have resulted in "life-saving drugs" that treat cancer and infectious diseases.[97] Modified nucleosides can function as "anticancer or antiviral agents because they are similar enough in structure to naturally occurring nucleosides that cells are tricked into accepting them, but are different enough to disrupt cell functioning and replication once inside the cell."[98]

Because of the potential application of modified nucleosides to disease treatment, chemists have been looking for biologically active nucleoside analogs "at least since the 1960s."[99] However, from the 1960s to the 1980s the synthesis of biologically active nucleoside analogs "was largely a matter of serendipity."[100] Moreover, during the early 1980s, "fluorine chemistry as applied to the nucleoside field was relatively new, and little

[91] Eli Lilly & Co. v. Sicor Pharm., Inc., 705 F. Supp. 2d 971.
[92] *Id.* at 975.
[93] *Id.* at 979.
[94] *Id.*
[95] TRUDY MCKEE & JAMES R. MCKEE, *supra* note 74, at 393-94.
[96] Piet Herdewijn, *Preface* of MODIFIED NUCLEOSIDES: IN BIOCHEMISTRY, BIOTECHNOLOGY AND MEDICINE, at XIX (Piet Herdewijn ed. 2008).
[97] *Id.*
[98] Eli Lilly & Co., 705 F. Supp. 2d at 979.
[99] *Id.*
[100] Piet Herdewijn, *supra* note 96, at XIX.

was known about how one might synthesize difluorinated nucleosides."[101] The key difficulty in synthesizing gemcitabine was incorporating the two fluorine atoms at the C-2' position of the sugar group (see Figure 2).[102] Even years after Eli Lilly produced gemcitabine, one medicinal chemist wrote, "the synthesis of fluorinated nucleosides is still a difficult task."[103]

2. The Race for Gemcitabine

Researchers at the Sloan-Kettering Cancer Center began investigating the biological activity of fluorinated nucleosides in the 1960s.[104] These efforts resulted in fluorinated nucleoside analogs 2'-F-ara-C[105] and 2'-F-cytidine,[106] which possess a single fluorine atom attached to the 2' carbon on the sugar ring (Figure 3). While these compounds exhibited promising anticancer activity,[107] they were not fully examined for their medical utility until the late 1970s and early 1980s.[108]

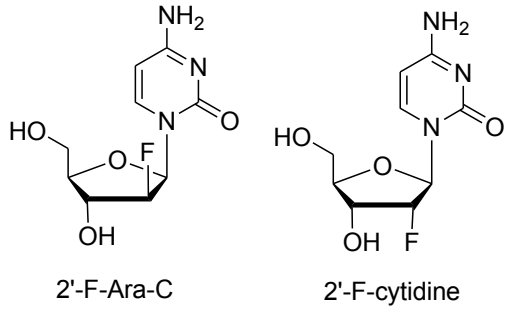

Figure 3: Structures of 2'-F-ara-C and 2'-F-cytidine

In the 1980s, the application of fluorine chemistry to nucleosides still remained largely unexplored.[109] In particular, little was known about how to synthesize nucleosides possessing two fluorine atoms attached to the same carbon (a geminal fluorine group).[110] Dr. Mirslav Bobek, a medicinal chemist at Roswell Park Memorial Institute in Buffalo, New York, spent most of his career developing methods to access therapeutic nucleoside analogs.[111] As shown in Figure 4, Dr. Bobek was successful at attaching two fluorine atoms to the carbon atom outside of the sugar (called a gem-difluorosaccharide).[112] However, he was unable to extend this methodology to the synthesis of gemcitabine and

[101] Eli Lilly & Co., 705 F. Supp. 2d at 980.
[102] *Id.*
[103] *Id.*
[104] *Id.* at 981.
[105] A. Kyoichi et al., *Nucleosides. 110. Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuranosylpyrimidine Nucleosides*, 22 J. MED. CHEM. 21, 21-22, (1979).
[106] Iris L. Doerr & Jack J. Fox, *Nucleosides. XXXIX. 2'-Deoxy-2'-fluorocytidine, 1-ß-D-ArabinofuranosyI-2-amino-l,4(2H)-4-iminopyrimidine, and Related Derivatives*, 32 J. ORG. CHEM. 1462, 1462-68 (1967).
[107] Eli Lilly & Co., 705 F. Supp. 2d at 1002.
[108] *Id.* at 981.
[109] *Id.* at 980.
[110] *Id.*; *see also* R. A. Sharma et al., *Synthesis of Gem- Difluorosaccharides*, 95 TETRAHEDRON LETT. 3433, 3433 (1977).
[111] Eli Lilly & Co., 705 F. Supp. 2d at 982.
[112] R. A. Sharma et al., *supra* note 110, at 3434-35.

eventually abandoned his efforts towards the blockbuster drug.[113] Dr. Donald Bergstrom[114] also aimed his synthetic efforts towards gemcitabine.[115] While he was able to synthesize a 3',3'-gemdifluoronucleoside (shown in Figure 5),[116] like Dr. Bobek, he never prepared gemcitabine and also abandoned his attempts for other nucleoside analogs.[117]

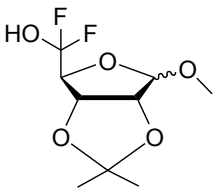

Figure 4: Bobek's gem-difluorosaccharide

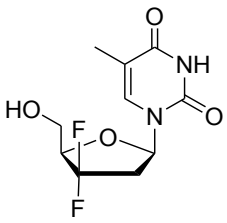

Figure 5: Bergstrom's 3',3-gemdifluoronucleoside

Like the many researchers probing the bounds of fluorine chemistry as applied to therapeutic nucleosides, Eli Lilly pursued fluorinated nucleosides and tried to license fluorinated compounds from Sloan Kettering.[118] When the parties could not reach a licensing agreement, Dr. Hertel, an Eli Lilly employee, proposed a new strategy to access geminal difluoronucleosides.[119] Dr. Hertel believed his methods would produce a nucleoside analog with two fluorine atoms at the C-2' position, even though his proposal was "dismissed by other researchers as a 'method of limited usefulness.'"[120]

The key step in Dr. Hertel's first proposed route to gemcitabine involved a Sharpless epoxidation reaction.[121] From May to September in 1981, Dr. Hertel attempted to synthesize a compound that would lead to gemcitabine by "[trying] at least four

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[113] For select publications regarding modified nucleosides from Dr. Bobek's laboratory, see J. Perman et. al, *Synthesis of 1-(2-deoxy-β-D-erythro-pentofuranosyl)-5-ethynyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (5-ethynyl-2'-deoxyuridine)*, 28 TETRAHEDRON LETT. 2427 (1976); Ram A. Sharma & Miroslav Bobek, *Acetylenic nucleosides. 1. Synthesis of 1-(5,6-Dideoxy-β-D-ribo-hex-5-ynofuranosyl)uracil and 1-(2,5,6-Trideoxy- β-D-erythro-hex-5-ynofuranosyl)-5-methyluracil*, 43 J. ORG. CHEM. 367 (1978); Miroslav Bobek & Vicki Martin, *The synthesis of anomeric 3-O-acetyl-5-O-benzoyl-2-azido-2-deoxy-D-arabinofuranosyl chlorides. Versatile sugar intermediates for the synthesis of 2'-azido-2'-deoxy- and 2'-amino-2'-deoxy-β-D-arabinofuranosyl nucleosides*, 22 TETRAHEDRON LETT. 1919 (1978).

[114] Professor of Chemistry at Purdue University. *See* Eli Lilly & Co., 705 F. Supp. 2d at 983.

[115] *Id.*

[116] Donald E. Bergstrom et al., *3',3'-Difluoro-3'-deoxythymidine: Comparison of Anti-HIV Activity to 3'-Fluoro-3'-deoxythymidine*, 35 J. MED. CHEM. 3369, 3369-72 (1992).

[117] Eli Lilly & Co. v. Sicor Pharm., Inc., 705 F. Supp. 2d 971, 983 (S.D. Ind. 2010).

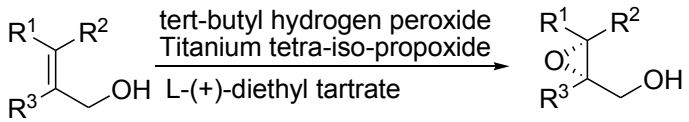
[118] *Id.* at 984.

[119] *Id.*

[120] *Id.*

[121] *Id.*; for the Sharpless epoxidation reaction mechanism, see JI JACK LI, NAME REACTIONS: A COLLECTION OF DETAILED REACTION MECHANISMS, 366-67 (2d ed. 2003).

Sharpless asymmetric epoxidaion reaction:



categories" of the epoxidation reaction.[122] When his efforts failed, Dr. Hertel consulted with renowned Drs. Barry Sharpless[123] and David Evans[124] who both thought Hertel's route would prove successful.[125] However, after months of failure, Hertel pursued a second, more direct route that used DAST as a fluorine source.[126] But this approach failed too. Hertel then investigated a new route using a Reformatsky reaction,[127] which finally produced the desired difluoronated intermediate needed to access gemcitabine (Figure 6).[128]

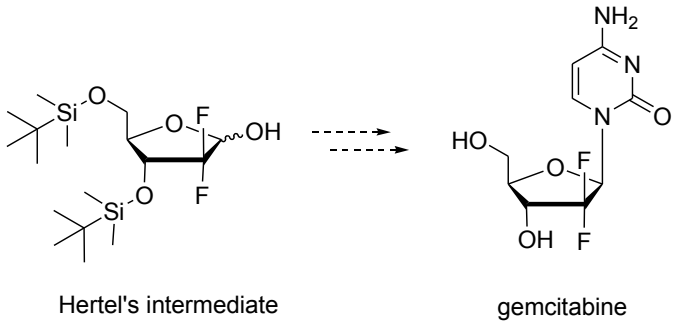


Figure 6: Hertel's advanced intermediate en route to gemcitabine

Despite Hertel's triumph in producing the difluorinated sugar, completing the final steps of the gemcitabine synthesis was not a simple matter. "Introduc[ing] fluorine into an organic molecule . . . significantly alters the chemistry of that molecule by deactivating some centers or activating others to reactions . . . so essentially, you had to kind of learn organic chemistry all over again."[129] As a result, Hertel spent the next nine months trying to convert his intermediate into gemcitabine.[130] Finally, in June 1982, Hertel completed the first total synthesis of gemcitabine[131] and its antiviral activity was demonstrated later that month.[132] Lilly filed its initial patent application for Hertel's fluorinated nucleoside on March 10, 1983.[133] Subsequent testing revealed gemcitabine's "unprecedented activity against a broad spectrum of cancers."[134]

3. The Aftermath of Gemcitabine's Successful Conclusion

[122] Eli Lilly & Co., 705 F. Supp. 2d at 984.
[123] Nobel Prize-winning chemist who developed the Sharpless epoxidation reaction. *See* http://www.scripps.edu/sharpless/ (last visted Jan. 6 2012).
[124] Professor of Chemistry at Harvard University. *See* http://www2.lsdiv.harvard.edu/labs/evans/index.html (last visited Jan. 6 2012).
[125] Eli Lilly & Co., 705 F. Supp. 2d at 984-85.
[126] *Id.* at 985.
[127] For the Reformatsky reaction mechanism, see LI, *supra* note 121, at 329.
[128] Eli Lilly & Co., 705 F. Supp. 2d at 985; L. W. Hertel et al., *Synthesis of 2-Deoxy-2,2-difluoro-D-ribose and 2-Deoxy-2,2-difluoro-D-ribofuranosl Nucleosides*, 53 J. ORG. CHEM. 2406 (1988).
[129] Eli Lilly & Co., 705 F. Supp. 2d at 985.
[130] *Id.*
[131] Dr. Robert Farr and Dr. Brian Metcalf at Merrell Dow Pharmaceuticals also explored numerous synthetic routes towards gemcitabine. Dr. Farr eventually synthesized the compound, but not until December 1984, at the earliest. *Id.* at 984.
[132] *Id.* at 985.
[133] *Id.*
[134] *Id.* at 987.

In 2010, generic pharmaceutical companies Sicor Pharmaceuticals, Inc. and Teva Pharmaceuticals tried to invalidate Lilly's patent on gemcitabine.[135] Of the many arguments set forth, the generic drug companies argued that Lilly's gemcitabine patent was obvious based on its structural similarity to prior art.[136] In particular, the defendants contended that anticancer agents Ara-C, 2'-F-cytidine, and 2'-F-ara-C, and (Figure 7) would have motivated a person of ordinary skill to synthesize Eli Lilly's blockbuster drug.[137] But the Southern District of Indiana was not persuaded. In upholding Lilly's gemcitabine patent, the court emphasized the (1) "track record of failure prior to Lilly's success with gemcitabine,"[138] and (2) long-felt need for treating pancreatic cancer,[139] "one of the most lethal cancers."[140]

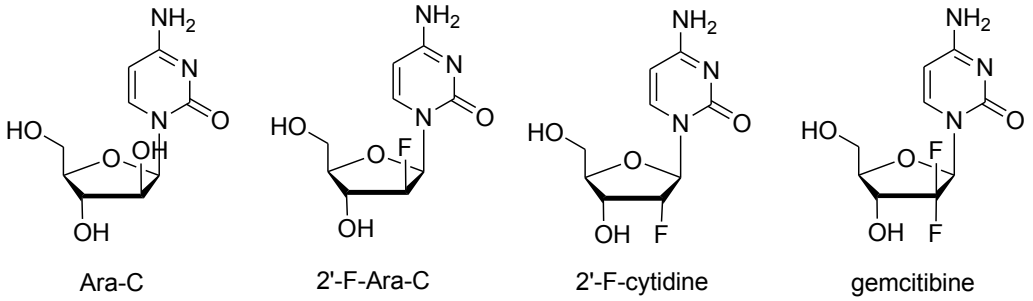


Figure 7: Ara-C, 2-F-Ara-C, 2'-F-cytidine, and gemcitabine

The defendant pharmaceutical companies attempted to "prove obviousness by virtue of gemcitabine's structural similarity" to Ara-C, 2'-F-cytidine, and 2'-F-ara-C (see Figure 7).[141] This argument did not convince the court. Though the structural similarities among these compounds may have been evident, the years spent formulating gemcitabine show that its realization was not a foregone conclusion. A given compound may be an obvious starting point for producing its structurally related analog, but it does not necessarily provide "meaningful precedent"[142] for the synthesis of its analogs. Visual similarity does not always translate into a straightforward route in the laboratory. Gemcitabine illustrates this point. Collectively, Drs. Bobek, Bergstrom, and researchers at Merrell Dow[143] spent many years investigating numerous synthetic routes to

[135] United States Patent No. 4,808,614. Eli Lilly & Co., 705 F. Supp. 2d at 975.
[136] *Id.* at 1001-04.
[137] *Id.* at 1001.
[138] *Id.* at 1009.
[139] *Id.* at 1008.
[140] Jennifer L. Spratlin & John R. Mackey, *Human Equilibrative Nucleoside Transporter 1 (hENT1) in Pancreatic Adenocarcinoma: Towards Individualized Treatment Decisions* 2 CANCERS 2044 (2010).
[141] Eli Lilly & Co., 705 F. Supp. 2d at 1002. Ara-C has a hydroxyl group (OH) "up" at the 2' position, while 2'-F-ara-C and 2'-F-cytidine have one fluorine atom at the C-2' position in the "up" and "down" position, respectively. Gemcitabine, on the other hand, possesses two fluorine atoms on the C-2' carbon.
[142] *Id.*
[143] Dr. Farr and Dr. Metcalf at Merrell Dow produced gemcitabine after Eli Lilly and failed to show that they conceived of the compound prior to Lilly. *Id.* at 996-97.

gemcitabine.[144] Yet, their "ultimately unsuccessful" attempts did not yield the compound or any nucleoside analog with two fluorine atoms at the C-2' position.[145] Thus, the court held that, "[i]n light of the fact that all of these methods were attempted and unsuccessfully so in the years leading up to and including the time that Lilly invented gemcitabine, it is abundantly clear that a person of ordinary skill in the art would have been uncertain as to how to synthesize gemcitabine."[146]

The need for a particular compound was also important to the obviousness analysis in *Eli Lilly*. Before the development of gemcitabine, only two drugs, fluorouracil (5-FU) and mitomycin, obtained FDA approval for the treatment of pancreatic cancer.[147] And only 5-FU had been approved for treating solid tumors at the time the gemcitabine patent application was filed.[148] While "5-FU in particular held some promise for survival benefit [for patients with pancreatic cancer]," it failed to "demonstrate a significant increase in survival or pain relief."[149] Moreover, the anticancer agents that defendant pharmaceutical companies proffered as prior art for gemcitabine were similarly ineffective. "Ara-C was 'good as an anticancer drug,' [but] its usefulness was limited to leukemia."[150] Likewise, 2'-F-cytidine, and 2'-F-ara-C had insufficient antitumor and antiviral activity and were abandoned by Sloan-Kettering "[b]ecause of such deficiencies."[151]

Unlike its predecessors, gemcitabine offers an improved one-year survival that is nine times better than the previous treatment for pancreatic cancer.[152] Since its FDA approval in 1996, gemcitabine has been used universally to treat around 1.5 million patients.[153] While gemcitabine has a "broad efficacy in humans against a variety of cancers,"[154] it remains the leading treatment advanced pancreatic cancer.[155] The court noted that the National Comprehensive Cancer Network made gemcitabine—not 5-FU—the "standard of care" for pancreatic cancer[156] and that gemcitabine exhibits an "improved capacity to kill cancer cells over Ara-C."[157] Furthermore, even though pancreatic cancer continues to have "the worst mortality rate and the lowest overall

[144] *Id.* at 999.
[145] *Id.*
[146] *Id.*
[147] *Id.* at 988.
[148] *Id.* at 1009.
[149] *Id.* at 988.
[150] *Id.* at 1003.
[151] *Id.*
[152] *Id.* at 979.
[153] *Id.*
[154] *Id.* at 987.
[155] *Id.* at 1008.
[156] *Id.*
[157] *Id.* at 987.

survival (OS) in all cancers,"[158] and gemcitabine is not a cure, "it was the first drug in thirty years to produce an improvement in overall survival."[159]

Given these facts, gemcitabine clearly filled a gap in cancer treatment. In discussing the long-felt need, the district court stated, "despite the existence . . . [of anticancer treatments before gemcitabine], the need for more effective chemotherapeutic agents for the treatment of solid tumors like those in pancreatic cancer still existed in the early 1980s."[160] As a result, patients with this disease "consistently faced a particularly negative prognosis because no chemotherapy was available that was effective as a treatment."[161] Thus, the district court held that "it is clear that gemcitabine met a long-felt need." The court's consideration of the long-felt need for effective cancer treatment speaks to the potentially large role that societal need can serve in the obviousness analysis. It follows that pharmaceutical patentees who develop a drug that fills a gap in medical treatment should survive an obviousness challenge—especially when coupled with the failure of others to mend that gap.

ii. Merck Sharp & Dohme Pharmaceuticals, SRL v. Teva Pharmaceuticals USA, Inc.[162]

Similarly, *Merck Sharp & Dohme Pharmaceuticals, SRL v. Teva Pharmaceuticals USA, Inc.* illustrates the influential role of (1) others' failure to bring an innovative drug to market; and (2) the long-felt but unmet need for a safe and effective drug in evaluating obviousness. The *Merck* case involved the development of Singulair®, an anti-asthma medication realized after years of research into the field of leukotrienes.[163,164] In an attempt to invalidate Merck's patent for montelukast, the active ingredient in Singulair®, Teva argued that the creation of montelukast was obvious in view of the prior art.[165] In upholding Merck's montelukast patent, the District Court for the District New Jersey reviewed the history of leukotriene research, considered the need created by the asthma epidemic, and ultimately disagreed with Teva's obviousness argument.[166]

1. Background of Leukotrienes Chemistry and Biology

[158] The occurrence of pancreatic cancer has "increased with 42,470 predicated new cases in the United States in 2009, in which 35,240 [people] will die." Xianjun Yu et al., *Targeted Drug Delivery in Pancreatic Cancer*, 1805 BIOCHIM. BIOPHYS. ACTA 97, 97-98 (2010).
[159] Eli Lilly & Co., 705 F. Supp. 2d at 1008.
[160] *Id*. at 988.
[161] *Id.*
[162] No. 07-1596 (GEB)(DEA), 2009 WL 3153316 (D.N.J. Aug. 19, 2009).
[163] *Id.* at **18-21.
[164] For a discussion regarding leukotriene chemistry, see R. N. Young et al., *Design and Synthesis of Sodium (βR*,γS*)-4-[[3-(4-Acetyl-3-hydroxy-2-propyl-phenoxy)propyl]thio]-γ-hydroxy-β-methyl-benzenebutanoate: A Novel, Selective, and Orally Active Receptor Antagonist of Leukotriene D_4*, 29 J. MED. CHEM. 1573, 1573 (1986) and references within; leukotrienes are produced in organs, like the lungs, and mediate the body's response to asthma triggers.
[165] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *48.
[166] *Id.* at **48-54.

"The leukotrienes story begins in the 1930s and 1940s" [167] when two physiologists discovered that the guinea pig lung produces a substance that causes the smooth muscle tissue in the lungs to contract.[168] This substance was later called slow-reacting substance of anaphylaxis, or SRS-A.[169] Scientists hypothesized that SRS-A was also produced in humans and "play[ed] a critical role in human asthma."[170]

Even though research was initially impeded by SRS-A's limited availability, instability, and unknown structure, SRS-A nevertheless interested many researchers studying asthma.[171] For example, in 1973, scientists at Fisons Ltd. in England discovered FPL-55712, a compound that prevented SRS-A from causing contractions in the smooth muscle tissue, presumably by blocking SRS-A (see Figure 8).[172] However, despite this breakthrough, FPL-55712 was not an ideal drug candidate "because it was inactive when taken orally (the ideal mode of dosing any drug) and had a very short half-life in the body[,] even when it was given intravenously."[173]

In the late 1970s, E.J. Corey[174] and coworkers discovered that SRS-A was composed of three leukotrienes: leukotriene C_4 (LTC_4); leukotriene D_4 (LTD_4); and leukotriene E_4 (LTE_4).[175] These compounds act on a single common receptor,[176] with LTD_4 being the most potent compound[177] (see Figure 8 for structure of LTD_4). Considering that LTD_4 is the primary component of SRS-A, researchers theorized that asthmatic reactions would be prevented by developing a compound that would bind with the LTD_4 receptor, thus blocking LTD_4.[178]

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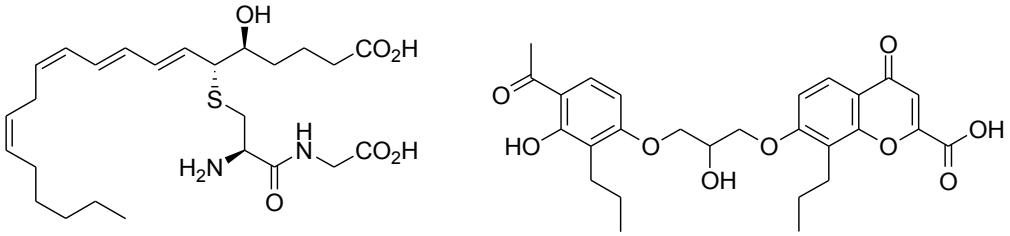
[167] Gleason, *supra* note 74, at 5.
[168] *See generally* William Kingsbury et al., *Leukotriene Receptors*, *in* 3 COMPREHENSIVE MEDICINAL CHEMISTRY 763-96 (Peter G. Sammes & John B. Taylor eds., 1990) (for a review article detailing status of leukotriene receptors through 1990); s*ee also* Gleason, *supra* note 74, at 5-18.
[169] Young, *supra* note 164, at 1573.
[170] Gleason, *supra* note 74, at 5.
[171] *Id.* at 6; Robert N. Young, *Discovery of Montelukast: a Once-a-Day Oral Antagonist of Leukotriene D_4 for the Treatment of Chronic Asthma*, 38 PROGRESS IN MEDICINAL CHEMISTRY 249, 250 (2001).
[172] J. Augstein, J. B. Farmer, T. B. Lee, P. Sheard, M. L. Tattersall, *Selective inhibitor of slow-reacting substance of anaphylaxis*, 245 NATURE 215 (1973); Robert N. Young, *supra* note 171, at 250.
[173] Gleason, *supra* note 74, at 6.
[174] Nobel Prize-winning chemist. *See* http://www.chem.harvard.edu/research/faculty/elias_corey.php (last visited Jan. 7, 2012).
[175] Gleason, *supra* note 74, at 6; *see also* Robert A. Lewis et al., *Slow Reacting Substances of Anaphylaxis: Identification of Leukotrienes C-1 and D from Human and Rat Sources*, 77 PROC. NATI. ACAD. SCI. USA 3710 (1980); Robert A. Lewis et al., *Identification of the C(6)-S-Conjugate of Leukotriene A with Cysteine as a Naturally Occurring Slow Reacting Substance of Anaphylaxis (SRS-A). Importance of the 11-cis-Geometry for Biological Activity*, 96 BIOCHEM. BIOPHYS. RES. COMMUN. 271-77 (1980).
[176] A receptor is a structure, typically a protein, which selectively binds to a molecule on the external surface of the cell. This interaction changes the cell's activity and starts a programmed response by the cell. For example, LTD_4 binds to the LTD_4 receptor and causes an inflammatory response in the body. *See generally* SILVERMAN, *supra* note 27, at 122-37.
[177] C. K. Buckner et al., *Pharmacological Evidence that Human Intralobar Airways Do Not Contain Different Receptors that Mediate Contractions to Leukotriene C4 and Leukotriene D_4*, 237 THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 558 (1986); *see also* Gleason, *supra* note 74, at 7.
[178] Gleason, *supra* note 74, at 6-7.



leukotriene D_4 (LTD_4) FPL-55712

Figure 8: leukotriene D_4 and FPL-55712

2. The Pursuit of a Safe and Effective Asthma Treatment

Armed with new structural and biological information about SRS-A and LTD_4, many pharmaceutical companies entered the global race for a safe and effective asthma treatment.[179] In the 1980s, medicinal chemists either: (1) modified the structure of LTD_4 or FPL-55712; or (2) screened for compounds showing promising activity.[180] Smith Kline & French ("SK&F"), now GlaxoSmithKline, initially modified the structure of LTD_4.[181] After substantial modifications and biological testing, SK&F synthesized a group of promising compounds.[182] SK&F 104353 (also called pobliukast, Figure 9), one of SK&F's most biologically useful compounds, advanced to clinical trials in humans.[183] However, SK&F terminated testing after pobliukast failed to show the required efficacy.[184] Scientists at SK&F subsequently reduced their work on in-house compounds after licensing another LTD_4 antagonist, pranlukast, from the Japanese company, Ono Pharmaceuticals (shown in Figure 11).[185]

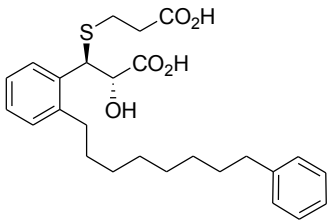


Figure 9: SK&F 104353 (pobilukast)

Eli Lilly explored a different route towards an LTD_4 antagonist by modifying the structure of FPL-55712.[186] Lilly developed a number of compounds with promising

[179] *Id.* at 7-8.
[180] Peter R. Bernstein, *Chemistry and Structure–Activity Relationships of Leukotriene Receptor Antagonists*, 157 AM. J. RESIR. CRIT. CARE MED. S220, S220 (1998).
[181] Gleason, *supra* note 74, at 8-10.
[182] Thomas W. Ku et al., *Synthesis and LTD_4 Antagonist Activity of 2-Norleukotriene Analogues*, 28 J. MED. CHEM. 1847 (1985).
[183] Gleason, *supra* note 74, at 10.
[184] *Id.*
[185] *Id.*
[186] *Id.* at 11.

biological activity,[187] but Lilly later abandoned the drug candidates after studies revealed liver toxicity in rats and mice.[188]

Imperial Chemical Industries ("ICI") focused on the structural similarities between both FPL-55712 and LTD_4 itself (see Figure 8 for the structures of FPL-55712 and LTD_4).[189] After substantial research and development, ICI synthesized zarfirlukast, which is sold under the brand name Accloate® by AstraZeneca (Figure 10).[190] While zarfirlukast has many positive qualities, it requires twice-a-day dosing[191] and has caused patients to suffer liver injury.[192]

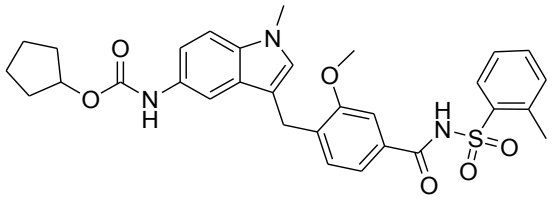


Figure 10: ICI 204219 (Accolate®)

Researchers at Ono Pharmaceuticals chose an alternative route by beginning their studies with the lead compound shown in Figure 11, which was probably selected through randomized screening.[193] In collaboration with SK&F, Ono developed pranlukast (ONO 1078).[194] SK&F subsequently abandoned their efforts towards pranlukast, while Ono pursued the compound and currently sells the drug in Japan (Figure 11).[195]

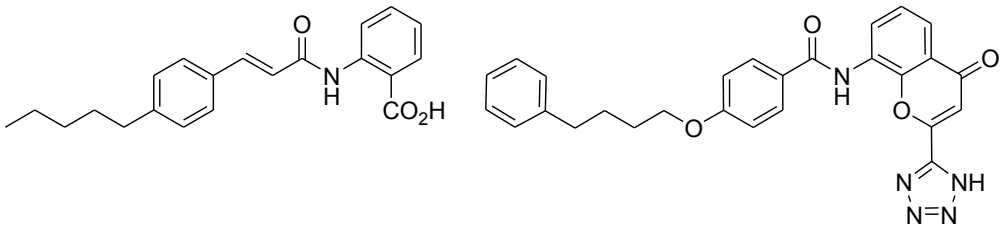


Figure 11: Ono's lead compound and pranlukast

Like Ono, researchers at Revlon Inc., Phone-Poulenc Rorer Pharmaceuticals Inc., and Wyeth Pharmaceuticals also chose a lead compound other than LTD_4 and FPL-55712

[187] *Id.*
[188] *Id.*
[189] *Id.*
[190] For the design and development of zafirlukast, see Bernstein, *supra* note 180, at S222-26.
[191] *Accolate Dosage*, EMEDTV, http://lungs.emedtv.com/accolate/accolate-dosage.html (last visited Jan. 10, 2012).
[192] John F. Reinus et al., *Severe Liver Injury after Treatment with the Leukotriene Receptor Antagonist Zafirlukast*, 133 ANN. INTERN. MED. 964, 964-67 (2000).
[193] *See* Bernstein, *supra* note 180, at S222.
[194] *Id.* at S221-22; Gleason, *supra* note 74, at 14.
[195] Gleason, *supra* note 74, at 14.

in the hopes of developing a better asthma treatment.[196] However, all companies abandoned their respective compounds due to safety and efficacy concerns.[197]

In 1979, Merck began their search for an asthma treatment by screening their chemical library for potential LTD_4 antagonists.[198] This resulted in a lead compound whose structure was similar to FPL-55712.[199] After substantial modifications and testing, Merck developed L-649,923 and L-648,051 (Figure 12).[200] These promising compounds exhibited excellent LTD_4 antagonist activity, but were ultimately abandoned due to insufficient efficacy.[201]

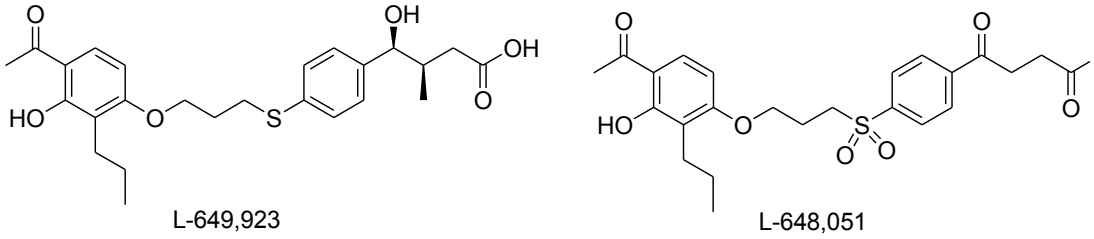


Figure 12: L-649,923 and L-648,051

"The Merck research team returned to the drawing board, identifying another lead compound by screening Merck's chemical library."[202] Merck chemists then modified a different lead structure to yield L-660,711, also known as MK-0571 (Scheme 1).[203] While L-660,711 showed promising activity in humans, safety studies revealed that the compound caused liver weight changes in animals, which could result in cancer.[204] Upon further analysis, Merck chemists found that only one of the enantiomers in L-660,711 caused the liver toxicity.[205] Thus, the other enantiomer, called verlukast, progressed to human clinic trials.[206] Verlukast, however, raised new liver toxicity concerns and was abandoned.[207]

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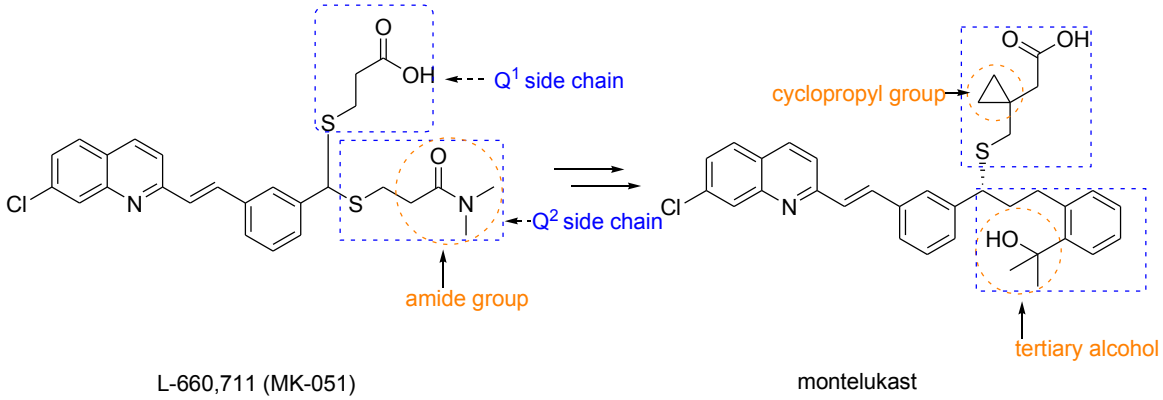
[196] *Id.* at 12-13.
[197] *Id.* at 13.
[198] Plaintiff Merck Sharp & Dohme Pharm., SRL's Pretrial Brief at 11, Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., No. 07-1596 (GEB)(JJH), 2009 WL 3153316 (D.N.J. Aug. 19, 2009).
[199] *Id.*
[200] *Id.*; *see also* T. R. Jones et al., L-649,923, *Sodium (βS*,γR*-4-(3-(4-acetyl-3-hydroxy-2-propylphenoxy)propylthio)-γ-hydroxy-β-methylbenzenebutanoate, a selective, orally active leukotriene receptor antagonist*, 64 CAN. J. PHYSIOL. PHARMACOL. 1068, 1068-75 (1986); T. R. Jones et al., *L-648,051, sodium 4-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propylsulfonyl]-γ-oxo-benzenebutanoate: a leukotriene D_4 receptor antagonist*, 64 CAN. J. PHYSIOL. PHARMACOL. 1535, 1535-42 (1986).
[201] Plaintiff Merck Sharp & Dohme Pharm., SRL's Pretrial Brief at 11, Merck Sharp & Dohme Pharm., SRL v. Teva Pharm. USA, Inc., 2009 WL 3153316 (2009) (No. 07-1596 (GEB)(JJH).
[202] *Id.*
[203] *Id.* at 12.
[204] *Id.*
[205] *Id.* L-660,711 was produced as a racemic mixture, an equal mixture of two molecules with the same chemical composition, but which exist as non-superimposable mirror images of one another (called enantiomers).
[206] Merck Sharp & Dohme Pharm., SRL v. Teva Pham. USA, Inc., No. 07-1596 (GEB)(DEA), 2009 WL 3153316, at *20 (D.N.J. Aug. 19, 2009).
[207] *Id.*

Despite earlier failures, Merck's chemists did not abandon their efforts towards a safe and effective LTD_4 antagonist. Because of its promising activity, chemists used L-660,711 as a foundation for further development.[208] Then, "[u]sing a trial and error approach," chemists made many structural modifications to L-660,711 (Scheme 1).[209] For example, replacing the sulfur atom in the Q^2 side chain with a carbon atom did not change the compound's potency.[210] Further studies showed that the amide group prevented the compound from remaining in the body for the desired timeframe.[211] To overcome this obstacle, chemists replaced the amide with a variety of other groups, and eventually found that incorporating a tertiary alcohol into the compound solved the short half-life problem.[212] But further modification was still needed to overcome the compound's toxicity problems.[213] The key was installing an additional carbon atom in the Q^1 side chain and attaching a cyclopropyl group at the beta-position.[214] These final changes resulted in montelukast[215]—a molecule that changed the world.[216]



Scheme 1: Formation of montelukast from L-660,711

3. Winning the Race: the Success of Montelukast

In an attempt to invalidate Merck's patent for montelukast, Teva argued that the montelukast patent was obvious in view of prior art.[217] Teva asserted that a person of ordinary skill in the art would have selected its lead compound (Scheme 2) as a starting point and converted it into montelukast through "at least eleven distinct steps."[218]

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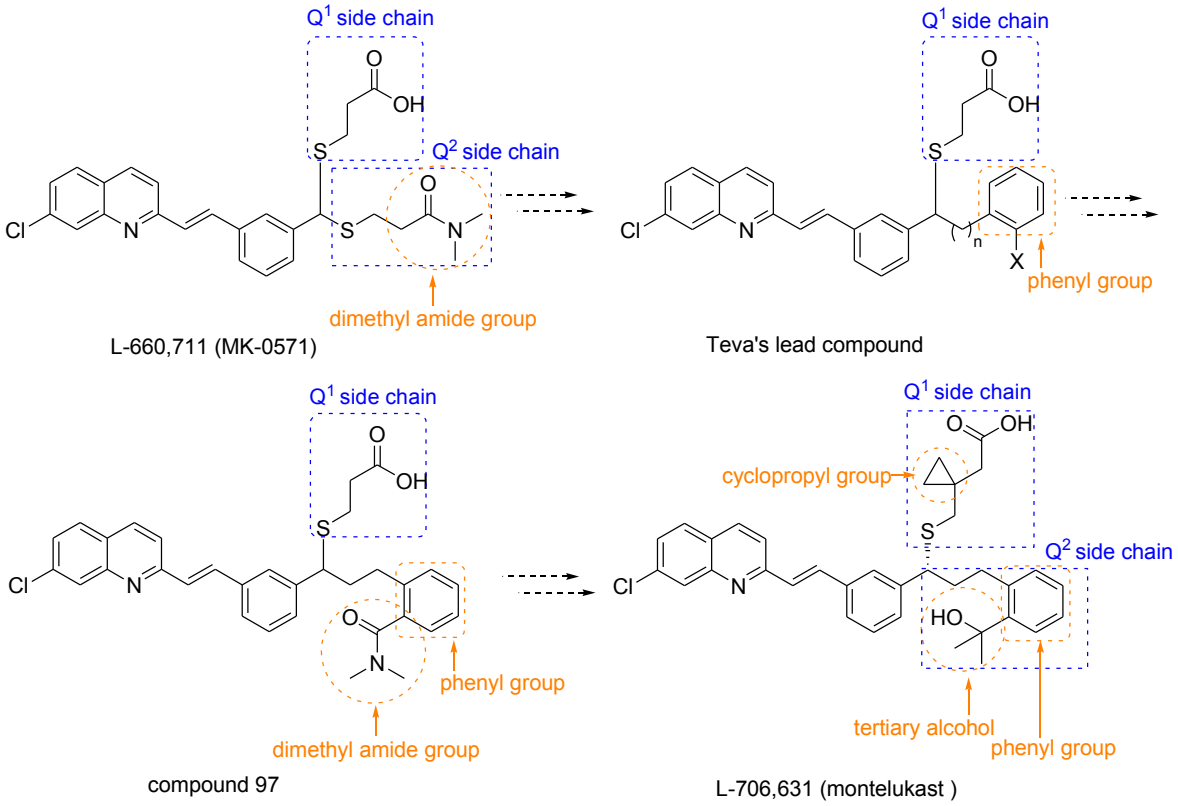
[208] *Id.*
[209] *Id.*
[210] *Id.*
[211] *Id.*
[212] *Id.* at **20-21.
[213] *Id.*
[214] *Id.*
[215] *Id.*
[216] K. C. NICOLAOU & T. MONTAGNON, MOLECULES THAT CHANGED THE WORLD, 114-17 (Janise Petrey ed., 2008).
[217] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at **48-49.
[218] *Id.* at *30.

Teva's proposed synthesis of montelukast begins by converting L-660,711 into Teva's lead compound (Scheme 2).[219] According to Teva's expert, Dr. George Lenz, it would have been obvious to modify the Q^2 side chain in L-660,711 by replacing the sulfur atom with a carbon atom, adding a phenyl group, and then attaching a substituent X to the phenyl ring.[220] Choosing a dimethyl amide for the "X" position in Teva's lead structure would yield compound 97,[221] a compound previously synthesized by Merck.[222] Continuing from this point, one must then decide to modify compound 97 by replacing the dimethyl amide with a tertiary alcohol, lengthening the Q^1 side chain, adding a cyclopropyl group to the beta position, and then resolving the enantiomers to yield the desired enantiomer of montelukast.[223]



Scheme 2: Teva's proposed synthesis of Montelukast from L-660,711 via Teva's lead compound

Teva's lengthy projected pathway from L-660,711 to montelukast did not convince the court that the road to montelukast was obvious. The structural similarity between Teva's lead compound and montelukast gives no indication of the immense effort required to bridge the gap between the two. For example, the installation of the

[219] *Id.*
[220] *Id.*
[221] *Id.*
[222] U.S. Patent No. 5,104,882; *see also* Plaintiff Merck Sharp & Dohme Pharm., SRL's Pretrial Brief at 29-33.
[223] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *30.

tertiary alcohol and the cyclopropyl group was no small feat. Replacing the dimethyl amide in L-660,711 with the tertiary alcohol in montelukast was initially met with skepticism.[224] Dr. Robert Young, the leader of the Merck leukotriene team, reasoned that even though tertiary alcohols and dimethyl amides are similar in size, the two moieties have different shapes "in the area where you would expect hydrogen binding to occur" and this dissimilarity in size "is [an] important difference."[225] Moreover, tertiary alcohols like the one in montelukast (called a benzylic tertiary alcohol) are characteristically unstable and "are expected to decompose in even mildly acidic conditions. So it is very unusual to see a tertiary alcohol on a drug [due to the human stomach's acidity]."[226] Likewise, "cyclopropyl groups were difficult to make and therefore were not commonly used [in drug development]."[227] Furthermore, Dr. John Gleason, the leader of SK&F's leukotriene program testified "that 'in this timeframe, 1990, cyclopropyl groups were not easy to make' and that '[c]yclopropyl is not commonly used.'"[228]

Further damaging to Teva's obviousness argument is that medicinal chemists from leading pharmaceutical companies used a variety of approaches to identify a lead compound.[229] Some researchers chose to modify the structure of the naturally occurring compound LTD_4, while others modified FPL-55712, and yet others fished for a lead compound from a chemical library.[230] This grab bag of approaches resulted in many promising compounds that never made it to market.[231] Dr. Gleason of SK&F later remarked that "over the period of about 12 years [SK&F] progressed several compounds into human clinical trials, but was unsuccessful in progressing a single leukotriene antagonist compound through to the market."[232] Likewise, "Eli Lilly & Co., Revlon, Rhone-Poulenc Rorer, [and] Wyeth Pharmaceuticals" all had compounds in "advanced stages of development" that were abandoned before commercial development.[233] Of Merck's many competitors, only Imperial Chemical Industries delivered a drug to the marketplace, although Accolate® has liver toxicity side effects.[234] Unlike its competitors, Merck was successful in bringing a safe and effective asthma treatment to market. Thus, the court could not ignore Merck's triumph amidst "the failure of others to develop a commercially useful leukotriene antagonist."[235] The court's decision in Merck's favor further strengthens the causal link between the failure of others and a ruling of non-obviousness. In 1998, the FDA approved the use of Singulair® tablets[236] to treat asthma in pediatric and adult patients and other dosages to treat allergic conditions such as

[224] *Id.* at *17, *28. Mr. Belley, the researcher who proposed adding the tertiary alcohol, was told by other Merck researchers that "he would be 'wasting his time"' because the tertiary alcohol was "not going to work."
[225] *Id.* at *29.
[226] *Id.*
[227] *Id.* at *15.
[228] *Id.* at *31.
[229] Gleason, *supra* note 74, at 7-18.
[230] *Id.*
[231] *Id.*
[232] *Id.* at 31.
[233] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *53.
[234] *Id.*
[235] *Id.*
[236] *Id.* at *34. The FDA approved Singular tablets in 5 mg and 10 mg quantities.

allergic rhinitis.[237] Asthma is a chronic disease, which causes inflammation of the lung airways. "The World Health Organization (WHO) estimated that 100-150 million people worldwide (equivalent to about half the population of the USA) were suffering from asthma in 2000, with the global death toll exceeding 180,000 per year."[238]

While asthma treatments existed before the development of Singulair®, the market had a long-felt need for a drug that had fewer side effects and was easier to administer. Traditional treatments such as inhaling steroids were ineffective at low doses and associated with "severe side effects at higher doses."[239] Moreover, long-acting beta antagonists must be used in combination with an inhaled steroid and carry a "black box" warning, which indicates side effects causing an increased chance of death.[240] Further, these "symptom-alleviating medication[s]" pale in comparison to Singulair®, which "prevent[s] the [asthma] attack from occurring in the first place."[241] As a result, the Merck court held that the "other drugs available prior to montelukast's inception showed significant shortcomings."[242]

The district court also refused to let other leukotriene-related drugs like Accolate® and Zyfo® stand in the way of Merck's blockbuster. Simply put, Accolate® and Zyfo® are not as safe and effective as Singulair®.[243] Accolate®, another leukotriene antagonist, must be taken twice a day, cannot be taken with food, and is plagued by liver toxicity issues.[244] Likewise, Zyflo®, a leukotriene inhibitor, must be taken four times a day and is also associated with liver toxicity.[245] On the other hand, Singulair® is "the only LTD_4 antagonist currently on the market that is indicated for once-a-day use."[246] Thus, the drug is easier to take than its competitors and is therefore advantageous for treating children.[247] Notably, the Global Initiative for Asthma (GINA) has recommended "montelukast as an accepted management therapy for the treatment of asthma."[248] As a result, the court concluded that "it is clear that montelukast fulfills a long-felt but unsolved need for asthma and allergic rhinitis sufferers."[249] This decision rightly elevates long-felt need to a position of importance in the obviousness analysis.

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[237] *Id.* Allergic rhinitis encompasses both seasonal and perennial allergic rhinitis. Like asthma, allergies occur when the body overreacts to allergens like pollen, pet danger, and dust mite residues. *See id.* at **17-18.

[238] K. C. NICOLAOU & T. MONTAGNON, *supra* note 216, at 114.

[239] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *34.

[240] *Id.*

[241] K. C. NICOLAOU & T. MONTAGNON, *supra* note 216, at 116. Singular binds with the leukotriene receptor, thereby blocking the leukotriene from initiating inflammation of the airways. Under normal circumstances, leukotrienes are produced to kill germs. However, the intended target is misconstrued in an asthma attack and body's own cells are destroyed, which damages the lung airways. *Id.* at 115-16.

[242] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *51.

[243] *Id.* at *52.

[244] *Id.*; for information regarding Accolate®, see http://www.astrazeneca.ca/documents/ProductPortfolio/ACCOLATE_PM_en.pdf.

[245] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *52; *Zyflo*, DRUGS.COM, http://www.drugs.com/pro/zyflo.html (last visited Jan. 11, 2012).

[246] Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *35.

[247] *Id.* at *52.

[248] *Id.*

[249] *Id.*

III. APPLYING SECONDARY CONSIDERATIONS TO ANALOGS: CRITICAL RESPONSE AND THE ROAD AHEAD

For several reasons, gemcitabine and montelukast are excellent case studies of the practical considerations impacting the obviousness of structurally related compounds. With an eye towards fulfilling a societal need in disease treatment, researchers in each case modified the structure of a lead compound to yield a drug that immensely benefited society. The methodical research process that produced gemcitabine and montelukast and the years of failed attempts that preceded their development are typical of drug discovery.[250] As such, these cases show that practical considerations such as the failure of others and long-felt need are especially relevant to the drug discovery process.

As is characteristic of courts considering the obviousness of structurally related compounds, both district courts placed primary emphasis on the unexpected efficacy and safety of gemcitabine and montelukast.[251] However, the district courts found additional support for non-obviousness in the failure of others and long-felt need. This fact is a necessary step towards acknowledging the important role of these secondary considerations in the obviousness analysis of structurally related compounds. However, the courts' opinions neglect to elevate these factors to a leading position in the analysis, which would be consistent with their applicability to the drug development process.

Going forward, when considering the obviousness of structurally related compounds like analogs, courts should place the utmost importance on the failure of others to develop a drug and the long-felt but unmet need that the drug fulfills. Because these factors are in step with the path of drug development, allowing pharmaceutical patentees to rely on these practical factors when seeking patent rights will encourage innovator firms to purse complex research and not abandon their efforts after disappointing results. "Many times during the course of human history, small molecules have cured tens of millions of people of serious diseases and improved the quality of life."[252] Surely the patentability of structurally related molecules should not turn on whether a researcher expresses surprise that one molecule is more effective as a treatment

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[250] *See* Peter R. Bernstein, *Chemistry and Structure—Activity Relationships of Leukotriene Receptor Antagonists*, 157 AM J. RESPIR. CRIT. MED. S220, S225 (1998) (commenting that in drug discovery, "[t]he synthesis of a new compound is merely the first step in a series of hurdles that, more likely than not, preclude a therapeutic agent from reaching the market. Identification of metabolites and degradation products, formulation and manufacturing issues, and, of course, safety and efficacy evaluations may lead to termination of a drug's development at any point . . . . [For example,] [f]rom the first discovery of SRS-A to the marketing of . . . [leukotriene antagonists such as zafirlukast and montelukast] took almost 60 years of effort by many dedicated people. Now those dedicated people have the opportunity to help those in need benefit from a new, safe, and effective treatment for asthma").

[251] *See* Eli Lilly & Co., 705 F. Supp. 2d 971, 1008 (S.D. Ind. 2010) (holding that [t]he evidence adduced at trial clearly shows that gemcitabine exhibited many surprising and superior characteristics in view of prior art, which support a finding that the invention would not have been obvious"); Merck Sharp & Dohme Pharm., SRL, 2009 WL 3153316, at *52 (placing emphasis on a researcher's testimony that "everybody was surprised to see [montelukasts'] activity").

[252] Ryoji Noyori, *Foreward* to MOLECULES THAT CHANGED THE WORLD, *supra* note 216, at viii (Janise Petrey ed., 2008).

than its analog. Scientific research that sets out to meet a need and succeeds in achieving it where others fail must be deemed equally, if not more, worthy of patent protection. By promoting the latter goal, courts will encourage scientists to work on hard problems whose resolutions can change lives for the better.

CONCLUSION

"Close involvement with society is the destiny of science."[253] Molecules that have a profound impact on society, like gemcitabine and montelukast, fulfill society's long-felt need to cure disease and improve the quality of life. Scientific research would be stifled if chemical patents could be invalidated merely because a compound resembles another previously developed or because a compound's properties aren't unexpected. Using pragmatic considerations such as the failure of others to produce a compound (itself a "superior indicator" of patentability[254]) and that compound's ability to meet a societal need can prove a powerful argument against obviousness. These factors will encourage inventors to continue along the path of discovery—even after years of wrong turns. Firms that conclude the race by delivering a needed drug to market should be compensated. Such were the cases of gemcitabine and montelukast.

In highlighting the underappreciated realities of the drug discovery process, the immense effort that precedes a drug's delivery to market, and the profound effect pharmaceuticals can have on disease treatment, this Note argues for the elevation of the failure of others and long-felt need in the obviousness analysis. Allowing researchers to rely on factors synchronized with the nature of chemical research for patent protection, rather than unpredictable results, will help drive pharmaceutical science. Because innovator drug firms rely on patent protection to fuel expensive and time-consuming R & D, the promise of a financial reward for developing a marketable drug is crucial to drug development. By rewarding companies that deliver effective drugs for diseases that plague society, patent laws have the power to encourage companies to persevere in the face of long odds.

[253] *Id.*
[254] Merges, *supra* note 48, at 866.