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Enantiomer Patents: Innovative or Obvious?

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I. Introduction

Stereochemistry relates to the spatial organization of atoms in a molecule. Often molecules having the same chemical makeup can exist in different spatial arrangements. These related molecules are known as stereoisomers. While stereoisomers have been studied since the 19th century, their impact on the safety and efficacy of pharmaceutical compounds was not readily appreciated until the 1970s. In fact, until a series of public health catastrophes forced the issue, isolating and administering a single stereoisomer was not a focus of research. Of particular interest were enantiomers. Enantiomers are a subset of stereoisomers, wherein two molecules exist as mirror images of each other, much like our right and left hands. As the potential benefits of administering a single enantiomer over a mixture of enantiomers were more understood, their popularity in the pharmaceutical industry grew. Today, enantiomeric drugs, constitute a significant portion of the prescription medications available to consumers, and are the active ingredients in such major brands as Lipitor, Plavix, Nexium, Azilect, and Nuvigil.

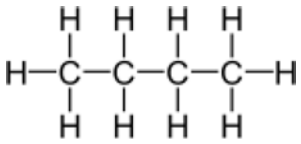
As the market value of enantiomeric drugs has grown, so too has the focus on the patents protecting them. In recent years, the validity of several patents claiming a single enantiomer have been challenged in the courts. Generally, the most germane issue in these cases turns on whether the claimed invention is an obvious variant of what previously existed. When assessing the obviousness of a patent claim, courts focus on four factors: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed subject matter and the prior art; and (4) objective evidence such as commercial success, long-felt need, and the failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). These factors are considered in order to determine whether a particular advance in technology is true innovation or the result of the normal progress, which is not subject to exclusive rights under the patent laws. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1746 (2007). In this article, we navigate recent obviousness challenges of enantiomer patents to determine how courts have applied these complex factual analyses in practice. Because these cases necessarily turn on intricate factual issues, the brief scientific primer below provides some context for the later legal discussion.

II. Scientific Background: A Primer for Non-Scientists

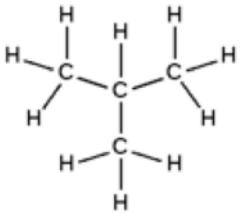
A molecule is a group of atoms held together by covalent bonds. Different molecules have different physical and chemical properties depending on their constituent atoms, the strength of the bonds between them, and their spatial arrangement. For instance, drinking pure water (H_2O) will keep you alive, drinking pure hydrogen peroxide (H_2O_2) could kill you, and drinking pure alcohol (C_2H_5OH) will do something else altogether.

Molecules that have the exact same formula, but different spatial arrangements, are known as isomers. For example, butane (C_4H_{10}) has two **constitutional isomers**: n-butane, where the four carbons are linked in a single chain, and isobutane, where three carbons are each linked to a central carbon.

n-butane



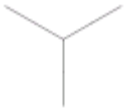
isobutane



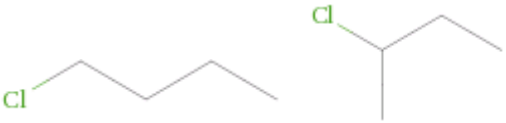
To simplify chemical drawings, chemists often omit hydrogen atoms (‘‘H’’), choosing instead to use skeleton diagrams containing carbon backbones and non-hydrogen groups. Carbons are found at the ends and bends of the black lines, hydrogen atoms are implied, and other atoms are always noted, as shown below.

n-butane

isobutane



chlorobutane 2-chlorobutane

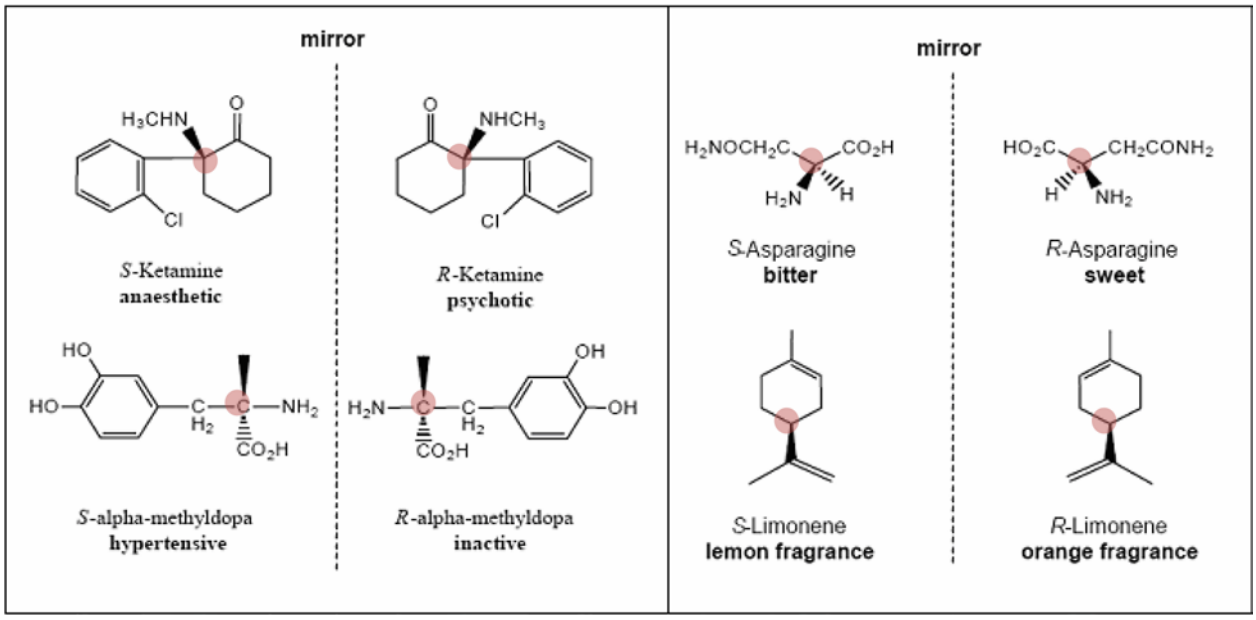


The more atoms in a molecule, the more isomers may occur. For example, $C_{20}H_{30}O_2$ is the chemical formula for dozens of distinct molecules, including abietic acid, isopimaric acid, pimaric acid, bosseopentaenoic acid, stenbolone, metenolone, and norethandrolone. Each of these isomers have different properties and interact differently with the human physiology.

Beyond constitutional isomers, there are also **stereoisomers**, which have the same structure, but a different spatial arrangement of atoms. **Enantiomers** are one type of stereoisomer particularly relevant to the pharmaceutical field. Enantiomers are molecules that have the same constituent atoms arranged in the same order, but are **non-superimposable mirror images** of each other, much like someone’s right and left hand. They are identical in almost every regard, except that they are asymmetric mirror images.

Enantiomers are characterized by the presence of a **chiral carbon**, a carbon atom attached to four distinct atoms or groups of atoms. While these molecules will have the same physical characteristics, *e.g.*, molecular mass, boiling point, and melting point, they may interact differently in the human body. For example, enzymes and other proteins can be particularly sensitive to enantiomers, resulting in different effects on the human physiology[1] (see ‘‘mirror’’ graphic).

[1] Chemistry: Introduction to Enantiomer Chemistry, UTEP College of Science, available at http://materialsworld.utep.edu/Modules/Concrete/Chromatography/Introduction%20to%20Enatiomer%20Chemistry/Introduction%20to%20Enatiomer%20Chemistry.htm (Chiral carbons are highlighted in shading) (To depict three-dimensionality in chemical formulas, a solid wedge is used for atoms projecting out of the plane of the molecule and a dashed wedge for atoms projecting into the plane)



Because chemical drawings are cumbersome, additional naming conventions exist to differentiate between enantiomers. One naming convention uses the spatial organization of the atoms at the chiral center to determine that molecule's **absolute configuration**. Once a chiral center is identified, the four substituents are then ranked according to established priority rules. Based on these rankings, the chiral center is designated either R (for *rectus*) or S (for *sinister*). Another classification uses an enantiomer to rotate polarized light. The enantiomer that rotates polarized light clockwise is labeled **(+)** or **dextrorotatory** and the enantiomer that rotates polarized light counterclockwise is labeled **(-)** or **levorotatory**. The (+) / (-) label has no fixed relation with R / S designation, as an R isomer can either be dextrorotatory or levorotatory depending on the substituents.

When a molecule has a single chiral center, and each R and S enantiomer is equally present as a 50/50 mixture, the composition is known a **racemate** or a **racemic mixture**. The process of isolating a particular enantiomer from that racemate is known as **resolution**. Alternatively, a single enantiomer can be synthesized directly by using chiral reactants.

As discussed above, the human body also has chiral receptors that may demonstrate preferences for one enantiomer of a molecule over the other. When the pharmacological activity of a molecule resides in a single enantiomer, the receptor (*e.g.*, enzyme) is said to be **stereoselective** as to that molecule.

III. Summary of Enantiomer Case Law

Over the past ten years, there have been a number of cases assessing the patentability of claims directed to a single enantiomer or pharmaceutical use thereof. In making their determinations, courts have looked at factors including: (i) whether the racemate was known in the prior art; (ii) the difficulty in resolving the enantiomer; (iii) the stereoselectivity of the relevant receptor; and (iv) other secondary considerations of non-obviousness such as commercial success, unexpected results, and satisfaction of long-felt needs in the art. Below is a summary of select cases discussing these factors.

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

At issue in *Aventis* was whether claims to a particular enantiomer of ramipril, an angiotensin-convertingenzyme (ACE) inhibitor demonstrating blood pressure-lowering effects, were obvious over the prior art teachings. Ramipril has five chiral centers, resulting in 32 different enantiomer arrangements, from RRRRR to RSRSR to SSSSS. *Id.* at 1295. The patent claimed only the SSSSS version of ramipril. *Id*. at 1296. The prior art taught a racemic mixture (SCH 31925) comprising the SSSSR and SSSSS enantiomers. *Id*. at 1300. It was also known that the relevant enzyme was stereoselective to the ''all-S'' enantiomers of similar molecules, such as captapril and enalapril. *Id*. at 1296-97, 1302. For example, the all-S enantiomer of enalapril exhibited a 700-fold increase in efficacy over other enantiomers. *See Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, 2006 WL 2008962 at *9 (E.D. Va. July 17, 2006).

The district court upheld the validity of the claims because, although it was a ''very close question,'' Lupin failed to show motivation to isolate (5S)-ramipril from the prior art racemate by clear and convincing evidence. *Id*. at *43. Prior to the resolution of Lupin's appeal, the Supreme Court decided *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), which advises against a rigid use of the ''teaching, suggestion, or motivation'' (''TSM'') test. Under *KSR*, the Federal Circuit needed only find ''some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness'' surrounding the isolation of SCH 31925's enantiomers. *Aventis*, 499 F.3d at 1301.

On appeal, the Federal Circuit found the claims to the ''all-S'' enantiomer of ramipril invalid as obvious because ''the close structural analogy between [ramipril enantiomers] and [enalipril enantiomers] would have led a person of ordinary skill to expect [ramipril enantiomers] to *differ similarly* in potency.'' *Id*. at 1302 (emphasis added). Additionally, the court found:

> ''. . . if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.''

Id. at 1301. Moreover, the Court found that the process of resolving racemic SCH 31925 into its enantiomers could be carried out ''by conventional chromatographic or fractional crystallization methods.'' *Id*. at 1302.

B. Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008)

The court in *Sanofi* analyzed the validity of claims to S-clopidogrel (Plavix), a thienopyridine derivative used for inhibiting blood platelet aggregation, which prevents blood clotting. *Sanofi* at 1078. The prior art included a patent for a class of thienopyridine derivatives covering thousands of possible molecules. *Id*. at 1079. One named example in the prior art, PCR 4099, was the racemic mixture of both enantiomers of clopidogrel. *Id*. at 1080.

Despite the disclosure of the racemate in the prior art, the court found that the resolution of *S*-clopidogrel was not simple or routine, and that the pharmacological properties of the resultant enantiomers were unpredictable. *Id*. at 1088 (internal quotations omitted). The district court had described the resolution as a ''paradigm of trial and error . . . neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained . . . and, if obtained, they could not have predicted by what method and configuration.'' *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F. Supp. 2d 353, 370-71 (S.D.N.Y. 2007) (''*Sanofi III*'').

Additionally, the clopidogrel enantiomers exhibited *absolute stereoselectivity*, *i.e.*, *S*-clopidogrel provided ''all of the favorable antiplatelet activity but with no significant neurotoxicity, while the [*R*-enantiomer] produced no antiplatelet activity but virtually all of the neurotoxicity.'' *Sanofi*, 550 F.3d at 1081. The court found this was especially surprising considering the other drugs in the class exhibited no stereoselectivity in regard to efficacy and toxicity. *Id*.

The district court also found ‘‘[a] person of ordinary skill in the art in the mid-1980s would have known that the enantiomers of a racemate could exhibit different biological activity—including different levels of both therapeutic activity and toxicity . . . where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong—a view confirmed by experts from both parties and credited by this Court.’’ *Sanofi III*, 492 F. Supp. 2d at 367.

C. Pfizer, Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495 (D. Del. 2005)[2]

The patents at issue in *Pfizer* both related to atorvastatin (Lipitor), a well-known statin used for lowering blood cholesterol. Similar to Sanofi, the prior art disclosed the same compound class covering thousands of potential molecules. *Pfizer*, 405 F. Supp. 2d at 502-04. Here, the court found that ‘‘there is nothing in the [prior art] patent expressing a preference for that compound as opposed to the thousands of other individual compounds identified by the [prior art] patent.’’ *Pfizer*, 405 F. Supp. 2d at 517.

Additionally, the district court found that there was no motivation to separate the racemic mixture into its enantiomer: ‘‘[T]he resolution of racemates into their individual isomers yielded, at best, an expectation of a two-fold increase in activity. This modest increase in activity was offset by the difficulty and complexity of the resolution process, as well as the reduced yield and increased waste disposal problems.’’ *Id*. The court also found that objective indicia of nonobviousness fell in favor of Pfizer, including the medical and commercial success of Lipitor providing evidence of a long-felt need and failure of others, *id*. at 518.

D. Forest Labs, Inc. v. Ivax Pharm., Inc., 438 F. Supp. 2d 479 (D. Del. 2006), aff’d 501 F.3d 1263, 1267 (Fed. Cir. 2007)

The Federal Circuit in *Forest Labs* affirmed the lower court’s finding that a claim to the S-citalopram (a selective serotonin reuptake inhibitor (SSRI) class antidepressant) was not obvious in view of the prior art.

Again, the prior art taught the racemic mixture, but the district court found that resolving S-citalopram from the racemate presented significant difficulties. *Forest Labs, Inc.*, 438 F. Supp. 2d at 488-94. The district court supported its conclusion that the resolution of S-citalopram resolution was challenging, risky, and required significant experimentation in view of the ‘‘lack of documented successes in achieving this resolution,’’ among other things. *Id*. at 493. Additionally, secondary considerations such as superior efficacy and commercial success as compared to the racemic mixture, also weighed in favor of the patentee. *Id*. at 495.

E. Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc., 348 F. Supp. 2d 713 (N.D. W.Va. 2004)

The court in *Ortho-McNeil* found that claims to levofloxacin were not obvious in view of the prior art. Here, the racemic mixture, ofloxacin, was disclosed in the prior art and the court recognized ofloxacin as the nearest prior art. *Ortho-McNeil*, 348 F. Supp. 2d at 750. Additionally, the court found that there was sufficient evidence to show that a person of ordinary skill would be motivated to resolve racemic ofloxacin, but there was no reasonable expectation to successfully resolve the enantiomers from the racemic mixture. *Id*. at 752, 754- 55.

In this case, Co-Plaintiff Daiichi held U.S. Patent No. 4,382,892 that covered the racemic ofloxacin molecule. *See id*. at 721. They argued that resolving ofloxacin proved especially difficult, having floundered at the effort for three years. *Id*. at 753. At trial, it was shown that the researchers initially charged with the project had no prior lab experience with enantiomeric separation. *Id*. However, at least four other companies succeeded in the resolution. *Id*. at 757-58. During prosecution of the patent at issue, the examiner rejected the claims on the basis that ‘‘[t]o resolve and identify the more

[2] The district court opinion in *Pfizer* was ultimately reversed on other grounds after the Federal Circuit found the claims at issue invalid under 35 U.S.C. §112. *Pfizer, Inc. v. Ranbaxy Labs Ltd.*, 457 F.3d 1284 (Fed. Cir. 2006) (“*Pfizer II*”). However, the district court opinion provides informative non-binding precedent regarding enantiomers in the 3rd Circuit.

active isomer is held to be within the skill of the worker in the art.'' *Id*. at 753. Due to these facts and others, the court found that the prior art sufficiently enabled the resolution of ofloxacin into levofloxacin. *Id*.

Despite this finding, there was also evidence that once resolved, levofloxacin had unexpected properties. Specifically, the court found that while increased activity or lower toxicity would not be surprising if found independently, the two increasing in concert was surprising because the prior art suggested an increase in activity would mean an increase in toxicity as well. *Id*. at 755. The court found most surprising that levofloxacin was ten times more soluble than ofloxacin, which was unprecedented when comparing racemates to their enantiomers. *Id*. The court also found that certain secondary considerations, such as unexpected results, commercial success, thirdparty praise and awards, copying, prior failure, fulfillment of long-felt need (modest weight given), weighed in favor of a finding of non-obviousness. *Id*. at 756-60.

F. Hospira, Inc. et al., v. Sandoz Inc., et al., 09-cv-4591-MLC, 2012 WL 1587688 (D.N.J. 2012)

The court in *Hospira* found claims to d-medetomidine (Precedex, a sedative) were not obvious in view of the prior art disclosing the racemic mixture. While the court found that the prior art would have motivated one of skill in the art to separate the enantiomers, there was no reasonable certainty at the time that such a separation could be successfully done. *Hospira* at *12, 14.

In finding non-obviousness, the court gave considerable weight to certain unexpected results. Particularly, that the relevant enzyme exhibited superior stereoselectivity to dmedetomidine compared to the racemate. *Id*. at *15-17. Additionally, the court found persuasive evidence of commercial success and prior art teachings that similar chemical analogues to medetomidine exhibited weak stereoselectivity when isolated into their enantiomers. *Id*.

IV. Discussion

As can be seen from the above cases, courts routinely engage in a detailed factual analysis when evaluating the obviousness of enantiomer patents. Particularly, these rulings have focused on the existence and selection of the racemate from the prior art; the decision to isolate one particular enantiomer; the complexity of separation; and the predictability of the results.

A. Selecting the Racemate From the Prior Art

The obviousness inquiry for enantiomers typically begins with the level of disclosure of the racemic mixture in the prior art. If the racemate is not expressly described in the prior art, then the issue of obviousness would likely fall under the Federal Circuit's ''Lead Compound'' precedent. *See Otsuka Pharm. Co. Ltd. v. Sandoz, Inc.*, 678 F. 3d 1280, 1291 (Fed. Cir. 2012) (stating that to resolve obviousness for ''new chemical compounds'', a court determines ''whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.''). If the racemate is disclosed in the prior art, the law is not entirely clear as to whether enantiomers are ''new chemical compounds'' to yield a Lead Compound analysis as set forth in *Otsuka*.[3]

Patentees — as would be expected — have argued that the lead compound requirement applies in enantiomer resolution determinations. In support, they often cite FDA regulations that consider enantiomers new chemical entities as compared to the racemate. Based on this rationale, patentees argue that before even turning to the issue of resolution, there must be clear and convincing evidence that one of skill would select the racemate as the lead compound to develop. To bolster their position, patentees often argue for a broad field of the invention, which can

[3] The analysis is further dependent on the claims at issue in the patent. For example, the ''Lead Compound'' analysis is traditionally reserved for compound claims, as opposed to method claims.

create a large number of potential drug candidates, requiring the use of hindsight to select the racemic mixture at issue from this broad field.

On the other hand, accused infringers — again as expected — argue that a ''Lead Compound'' analysis is not a part of enantiomeric obviousness cases. In support, they point out that the enantiomer is present, but just not isolated, in the racemate. The premise here is that the determination of obviousness should begin with recognizing the disclosed racemate as a viable candidate for development.

In light of *KSR*'s admonition against bright-line rules, the description of the racemate in the prior art is perhaps best considered in terms of degree.[4] A broad, general description of a racemate, not singled out from other prior art compounds by any measure, would tend toward a finding of non-obviousness. On the other hand, a specific identification of a racemate as a promising compound would support an obviousness conclusion. This approach, in addition to being consistent with *KSR*, is rooted in common sense. Requiring a lead compound in a broad field suggests that there is only one obvious path forward in each field, which is inconsistent with science's methodical progress down multiple paths. On the other hand, not requiring any reason in the prior art to select the racemate as promising for further development would nullify inventive breakthroughs.

In the cases summarized above, the racemate was disclosed in the prior art to some extent. However, the specific level of identification varied from the racemate being disclosed in list of potential compounds to the racemate being specifically identified as a chiral molecule having positive features suggesting potential development.

B. The Decision to Isolate

Because the science and knowledge surrounding racemates and their component enantiomers has evolved over time, the priority date of the patent at issue is critical to obviousness analysis. For this same reason, earlier decisions, which focus on different time periods, may no longer be as persuasive. The trend seems to be toward finding a motivation to isolate the enantiomers of an identified racemate. *See Hospira* at *12, 14. This may stem from a number of converging teachings in the prior art. First, as mentioned above, the potential for an isomer to have unique properties has become more well publicized. Also, the FDA has released guidelines regarding stereoisomeric drugs. Development of New Stereoisomeric Drugs, May 1, 1992 FDA Guidance (available at http://www.fda.gov/drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/ucm122883.htm). While not requiring isolation of enantiomers, these guidance documents provide evidence of potential motivations a formulator would have to isolate enantiomers for study.[5]

In addition to looking generally at whether isolation might be appropriate, it can also be appropriate to look at whether the stereochemistry of other members of the class of molecules being considered is relevant to their safety or efficacy. If so, it would follow that those of skill in the art would be motivated to review the biological impacts of the molecule's stereochemistry. On the other hand, a lack of stereochemistry effects in similar molecules could bolster a finding that the decision to isolate a particular enantiomer was more innovative, and thus, potentially non-obviousness. Similarly, knowledge of stereoselectivity in the compound's physiological target may provide motivation to resolve a racemic mixture in the prior art. For instance, many of the drugs in the previously mentioned cases target proteins or enzymes, (*e.g.*, selective serotonin reuptake inhibitors (SSRI), angiotensin-converting-enzyme (ACE) inhibitors). If those enzymes

[4] *KSR*, 127 S. Ct. at 1741 (''Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.'')

[5] This is not to suggest that other external or implicit motivation to resolve chiral molecules may be found before or after these FDA recommendations.

were known to be stereoselective, it may be obvious to one skilled in the art to evaluate a set of enantiomers for the optimal safety and efficacy.

C. Difficulty of Resolution

A third focus of the obviousness inquiry is the difficulty of resolution. While Louis Pasteur was able to resolve racemates as early as 1848, the unique, and increasingly complex, spatial and chemical characteristics of new and different molecules may present novel challenges to drug developers even today. Further, methods for isolating enantiomers has evolved over time. Therefore, consideration of the specific facts of the case are important. The impact of this factor is straightforward — the more difficult the resolution, the more non-obvious, and vice versa, but the factual distinctions between the cases may not be readily apparent without expert consultation.

D. Secondary Considerations of Non-obviousness

Finally, courts have considered the secondary considerations of non-obviousness. Of these, unexpected results are often heavily debated between the parties and cited by courts. Prior to *In re Cyclobenzaprine*, some courts applied a regimented obviousness analysis where the first three factors were considered to determine whether a *prima facie* case was met before turning to secondary considerations and unexpected results to determine whether that case was rebutted. In *In re Cyclobenzaprine*, the Federal Circuit clarified that this methodology was not optimal. Instead, unexpected results should be considered along with all of the other factors to answer the overarching, fundamental question of whether an invention is obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 107880 (Fed. Cir. 2012) *cert. denied*, 133 S. Ct. 933, 184 L. Ed. 2d 725 (U.S. 2013).

Thus, unexpected results, in and of themselves, are not a panacea for patentees, or a death knell for those challenging enantiomer patents. Rather, they should be considered along with the other *Graham* factors. Further, the value of the unexpected results, especially in relation to any reasonably expected result, should be weighed in the obviousness analysis. For example, if an enantiomer is expectedly safer and also unexpectedly more effective, perhaps it is obvious because one of skill in the art would have been motivated to achieve the enantiomer for the expected safety. In that example, the known problem of safety is arguably solved by the resolution. *See KSR*, 127 S. Ct. 1742 (‘‘One of the ways in which a patent’s subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent’s claims’’).

The cases above also show that patent challengers often rely on the behavior of similar chemical analogs to support their position of expected results. However, this line of attack has its pitfalls, because courts often struggle in ascertaining the appropriate level of similarity necessary to justify an expected result. Thus, the importance of qualified chemical expert witnesses prove critical to such a defense. Put simply, parties should carefully consider both expected and unexpected results when evaluating their obviousness positions.

V. Conclusion

Determination of obviousness requires specific consideration of the facts and circumstances in each case. In this article, we have identified some of the facts that are most often cited in determining the validity of patents claiming enantiomers and their methods of use. The following chart summarizes some of the considerations in each case and the highest court's determination:

Case	Molecule	Was the Racemate Taught in the Prior Art	Did the Prior Art Class Exhibit Stereochemical Dependent Effects?	Difficulty in Resolution	Secondary Considerations Presented	Invalid as Obvious?
Aventis	Ramipril	Yes	Yes	Low	commercial success; long-felt need; unexpected results (against placebo); copying	Yes
Sanofi	Clopidogrel	Yes	No	High	unexpected results; failure of others; long-felt need; commercial success; copying	No
Pfizer	Lipitor	Yes	Weakly	High	commercial success; long-felt need; failure of others; copying	No
Forest Labs	Citalopram	Yes	Weakly	High	commercial success; unexpected results; copying	No
Ortho-McNeil	Levofloxacin	Yes	Weakly	Very High	unexpected results; commercial success; third-party praise and awards; copying, prior failure; fulfillment of long-felt need (modest weight given)	No
Hospira	Medetomidine	Yes	Weakly	High	unexpected results; commercial success	No

As can be seen historically, the majority of the cases considering the obviousness of enantiomers have found them non-obvious. But future obviousness determinations may not follow these precedents because science, and what is obvious, evolves over time. For example, the evolution of skill in the art may be why a more recent case like *Hospira* finds a motivation to isolate an enantiomer, whereas the earlier *Forest Labs* court found no such motivation. Given the number of enantiomeric products being sold and in pipelines, the only thing that is fairly certain is that these issues will be hotly litigated in the future.