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I. INTRODUCTION

Pharmaceutical research and development is an unpredictable business. The harsh reality is that for every five-thousand to ten-thousand compounds made in the laboratory, only one goes on to become a marketed product.[1] Furthermore, the research and development process, from initial identification of a therapeutic target to product launch, takes on average, ten to fifteen years.[2] The average estimated cost to bring a pharmaceutical product to market is 1.3 billion dollars.[3] Such investments of time, resources, and money are justified in the face of that unpredictability because of the potential financial rewards of a successful product. Those financial rewards can be obtained if the drug developer can clear the rigorous hurdles of the United States Patent and Trademark Office (USPTO) and the United States Food and Drug Administration (FDA). Once cleared, the drug developer is awarded statutory exclusionary rights, for a finite period of time, to market its approved product.

To satisfy the requirements for obtaining justified U.S. patent protection, the developer's drug must be novel. But even if novel, the drug must also be nonobvious. Sometimes, the chemical structure or solid state form of the drug comes as if it were a thunderbolt out of the blue, radically departing from the structures or solid state chemistry of prior drugs. In other cases, however, innovation is a gradual process, and it is possible that each such gradual advance will build incrementally on what is already known.

Even subtle differences in the framework United States courts apply to determine whether novel advances over the art are nonobvious, a requirement for patentability, have a profound impact on which types of advances are rewarded with patent protection and which are not. It is the purpose of this article to see if and how, in the context of the innovative pharmaceutical world, the United States Supreme Court in *KSR*

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[1] Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile 2008* 3 (PhRMA 2008).

[2] *Id.*

[3] *Id.* at 2.

International Co. v. Teleflex, Inc.[4] has affected how United States courts evaluate whether a novel scientific or technical advance is nonobvious over what was already known at the time of the advance. This article seeks to show how the *KSR* decision re-emphasized certain aspects of obviousness precedent in the U.S. and modified others.

In an effort to achieve that purpose, we consider the Supreme Court's *KSR* decision itself and then examine how it has been applied to pharmaceutical inventions by the Court of Appeals for the Federal Circuit (CAFC). We then examine certain actions innovative pharmaceutical companies should consider to demonstrate the nonobviousness of patents and patent applications post-*KSR*.

II. THE SUPREME COURT'S *KSR* DECISION

A. Background

Title 35 of the U.S. Code, Section 103(a) provides that a patent may not be granted when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." In *Graham v. John Deere Co. of Kansas City*, the Supreme Court set out a framework for applying the statutory language of § 103:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.[5]

In the years since *Graham* and before *KSR*, the CAFC[6] developed a framework for evaluating obviousness that came to be known as the teaching, suggestion, or motivation test ("TSM test"). Under the TSM test, a patent claim is only proved obvious if " 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of

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[4] 550 U.S. 398 (2007).

[5] 383 U.S. 1, 17-18 (1966).

[6] The CAFC has exclusive jurisdiction over all appeals in patent cases. 28 U.S.C. § 1295(a)(1) (2000).

the problem, or the knowledge of a person having ordinary skill in the art."[7] The CAFC came to rely on the TSM test as a way, and often as the only way, to bring objectivity to the obviousness inquiry. However, by the time the Supreme Court reached its decision in *KSR*, many critics had come to regard the TSM test as too rigid to adequately identify obvious inventions, leading to the grant of patents for proposals that critics considered to be unworthy advances.[8]

B. The Supreme Court Rejected a Rigid Application of the TSM Test

The patent at issue in *KSR* was quite different from a patent on new drugs, claiming the combination of an adjustable vehicle accelerator pedal assembly and an electronic sensor, attached to a fixed pivot point, which provides a signal corresponding to the position of the pedal.[9] Teleflex Inc. ("Teleflex"), the patent owner, sued KSR International Company ("KSR") for infringement in the U.S. District Court for the Eastern District of Michigan. The district court granted KSR's motion for summary judgment of invalidity for obviousness in view of the prior art, but the CAFC reversed and remanded, applying the TSM test to find a lack of sufficient motivation to combine the prior art references in view of the problem to be solved.[10] The Supreme Court in turn reversed the judgment of the CAFC and reinstated the district court's summary judgment of invalidity.

In *KSR,* the Supreme Court mandated a more flexible test than the TSM test, including the application of common sense and consideration of marketplace demands, such as the demand for accelerator pedals that can operate with computers.[11] The Court also cautioned that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."[12] But at the same time, the Court observed that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious," and that the Court had previously held a patent valid when "the elements worked together in an unexpected and fruitful manner."[13]

In *KSR*, the Supreme Court focused on predictability from the perspective of a person of ordinary skill in the art ("POSITA"). Prior to

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[7] *KSR*, 550 U.S. at 405 (quoting *Al-Site Corp. v. VSI Intl., Inc.*, 174 F.3d 1308, 1323-24 (Fed. Cir. 1999)).

[8] *See* Federal Trade Commission, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, A Report by the Federal Trade Commission* 12 (Oct. 2003) (available at http://www.ftc.gov/os/2003/10/innovationrpt.pdf).

[9] 550 U.S. at 406.

[10] *Id.* at 411-15.

[11] *Id.* at 415.

[12] *Id.* at 416.

[13] *Id.*

KSR, courts generally viewed a POSITA as someone who follows conventional wisdom and does not innovate. An example is provided by the CAFC's decision in *Standard Oil Co. v. American Cyanamid Co.*, where it characterized the POSITA as "presumed to be aware of all the pertinent prior art" in an obviousness analysis, but also as "presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which."[14] In contrast, the Supreme Court in *KSR* credited the POSITA with creativity, observing that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton."[15]

Because the POSITA is ordinarily creative, the Court observed that:

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.[16]

In the cases discussed *infra*, a determination of the metes and bounds of this new found creativity of a POSITA has not been in issue. Hence, the contours of whatever may result from that change in the nature of a POSITA must await future decisions.

III. APPLICATION OF *KSR* TO PHARMACEUTICAL INVENTIONS

A. Introduction

The CAFC has directly addressed the issue of obviousness in numerous appeals of pharmaceutical patent infringement cases shortly before and since the Supreme Court's *KSR* decision. In some of those cases, the CAFC concluded that the claims at issue were invalid as obvious,[17] while in a larger number of cases, the asserted claims were found

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[14] 774 F.2d 448, 454 (Fed. Cir. 1985).

[15] 550 U.S. at 420.

[16] *Id.* at 421.

[17] *See e.g. Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007); *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). *Pfizer* was decided just over one month before the Supreme Court's *KSR* opinion was issued. The *Pfizer* court was clearly influenced by the fact that the Supreme Court had granted *certiorari* in *KSR* and did not apply a strict version of the TSM test. *Pfizer* is discussed in detail below.

nonobvious.[18] In deciding those cases, the CAFC acknowledged that the unpredictability present in drug development tends to strongly favor patentability of pharmaceutical patent claims.

B. Drug Substances

When one thinks of a pharmaceutical invention, the first thing that comes to mind generally is the drug itself (i.e., the chemical compound that is the active ingredient). That drug is often termed a "New Chemical Entity" or "Drug Substance." Because science sometimes builds on prior success, scientists may discover a chemical compound useful as a drug substance by modifying the structure of previously known compounds or even previously known drugs. In those cases, the structure of the new compound is necessarily similar in many ways to those related compounds. However, that new drug substance also will differ in one or more ways from those previous compounds, and it is those differences that may impart patentability.

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, the CAFC affirmed the district court's judgment that the asserted claims of U.S. Patent No. 4,687,777 ("the '777 patent") were not obvious.[19] Takeda sued Alphapharm following Alphapharm's application to the FDA for approval to market a generic version of Takeda's type 2 diabetes medication ACTOS®.[20] The active ingredient in ACTOS is pioglitazone, which has the chemical name 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.[21]

Claim 1 of the '777 patent recited a compound based on its chemical formula. That compound includes an ethyl-substituted pyridyl ring, in which the ethyl group may be at any of four positions (i.e., the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound, or 6-ethyl compound).[22] Claim 2 depends upon claim 1 and specifies that the compound is pioglitazone, a compound with the 5-ethyl substitution and the approved drug substance.[23]

Alphapharm asserted that the '777 patent claims would have been obvious under 35 U.S.C. § 103 on the basis of a prior art disclosure of

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[18] *See e.g. Forest Laboratories, Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); *In re Omeprazole Pat. Litig.*, 536 F.3d 1361 (Fed. Cir. 2008); *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341 (Fed. Cir. 2008); *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008).

[19] 492 F.3d at 1352.

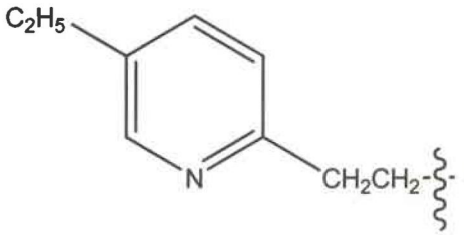
[20] *Id.* at 1354.

[21] *Id.*

[22] *Id.* at 1353.

[23] *Id.* at 1354.

"compound b."[24] Alphapharm argued that compound b is similar to pioglitazone, but it was not novelty defeating because the left moiety compound b consists of a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring. Thus, pioglitazone differs in two ways from prior art compound b in that the pioglitazone ring is substituted: (1) at a different position; and (2) by a different chemical group, as shown in the following illustration.[25] The portions of pioglitazone and compound b that differ are shown in the following diagrams:



Pioglitazone compound b

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103.

On appeal the CAFC affirmed, taking the opportunity to reiterate that its case law concerning the prima facie obviousness of chemical compounds is still applicable in view of *KSR*. Under the CAFC's approach, a finding of prima facie obviousness of a chemical compound requires: (1) structural similarity between the claimed compound and prior art compounds, which would lead a POSITA to choose a prior art compound as a lead compound for modification; and (2) a reason or motivation in the prior art for making the structural change to arrive at the claimed compound.[26] The CAFC then commented that its test for motivation to modify a known chemical entity is consistent with *KSR*, because the Supreme Court had indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis," because as "long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an obviousness inquiry."[27] Therefore, the CAFC reiterated that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to

[24] *Id.*
[25] *Id.* at 1360.
[26] *Id.* at 1356.
[27] *Id.* at 1357.

establish prima facie obviousness of a new claimed compound."[28]

The CAFC then applied that standard to Alphapharm's contention that the skilled artisan would have been motivated to modify compound b to arrive at pioglitazone. The CAFC summarized Alphapharm's argument as relying on two parts.[29] Initially, the skilled artisan would identify compound b as a lead compound for further modification.[30] Then, upon selecting that compound for antidiabetic research, the skilled artisan would have made:

> two obvious chemical changes; first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone.[31]

Regarding lead compound selection, the CAFC first reviewed the district court's finding that the prior art '200 patent disclosed hundreds of millions of compounds, and specifically identified fifty-four compounds, including compound b.[32] While the prosecution history had presented data for nine selected compounds, the CAFC agreed with the district court that there was:

> nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties.[33]

Another prior art document (the Sodha II reference) also factored into the CAFC's analysis.[34] That document disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds.[35] Those compounds did not include pioglitazone, but included compound b. The Court focused on the fact that "Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity," and that "compound b was not identified as one of the three most favorable compounds. On the contrary, compound b,

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[28] *Id.*
[29] *Id.*
[30] *Id.*
[31] *Id.*
[32] *Id.*
[33] *Id.*
[34] *Id.* at 1358.
[35] *Id.*

was singled out as causing 'considerable increases in body weight and brown fat weight.' "[36] On the basis of that evidence, the CAFC agreed with the district court that the three compounds identified by Sodha II, rather than compound b, would have been favored by the skilled artisan as starting points for further investigation.[37]

The CAFC also rejected Alphapharm's argument that the *KSR* decision mandated reversal of the district court. The CAFC observed that:

> [r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.[38]

The CAFC also approved of the district court's finding that "nothing in the prior art [suggested] making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds."[39] The CAFC pointed to the district court's reliance on expert testimony that "homologation had no tendency to decrease unwanted side effects" and that "the biological activities of various substituents were 'unpredictable' " based on the prior art.[40] Similarly, with respect to ring-walking, the CAFC noted that the district court found no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes.[41]

Later, in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, the CAFC likewise affirmed a district court's determination that a claimed chemical compound was nonobvious over the prior art.[42] At issue was Eisai's U.S. Patent No. 5,045,552 ("the '552 patent"). The '552 patent claims rabeprazole and its salts (collectively, "rabeprazole").[43] Rabeprazole is a proton pump inhibitor.[44] "Rabeprazole's sodium salt is the active ingredient

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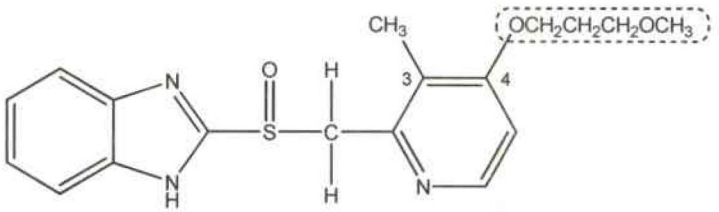
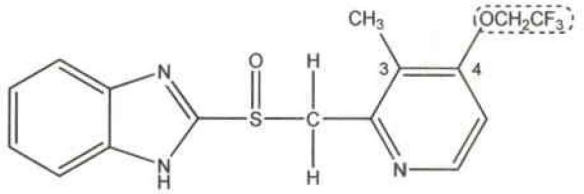
[36] *Id.*
[37] *Id.* at 1359.
[38] *Id.*
[39] *Id.* at 1360.
[40] *Id.* at 1360-61.
[41] *Id.* at 1361.
[42] 533 F.3d at 1362.
[43] *Id.* at 1356.
[44] *Id.*

in Aciphex[®], a pharmaceutical approved . . . for the treatment of duodenal ulcers, heartburn, and associated disorders."[45] Teva asserted that the '552 patent claims were obvious over a combination of three references: (1) a European patent claiming the anti-ulcerative compound lansoprazole ("EP '726"); (2) a U.S. patent claiming proton pump inhibitor omeprazole; and (3) an article by Brändström describing a class of anti-ulcerative compounds having a particular core structure in common between rabeprazole, lansoprazole, and omeprazole.[46]

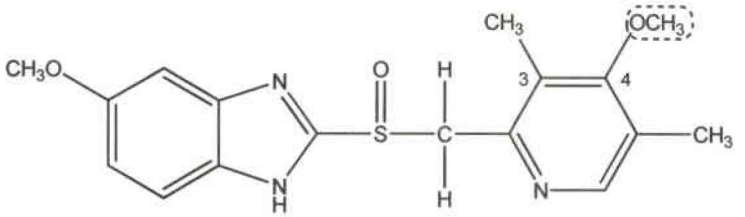
Lansoprazole differs structurally from rabeprazole at the 4-position on the pyridine ring; lansoprazole has a trifluoroethoxy ($-OCH_2CF_3$) substituent, whereas rabeprazole has a methoxypropoxy ($-OCH_2CH_2CH_2OCH_3$) substituent, as shown in the following representation:[47]



Rabeprazole



Lansoprazole



Omeprazole

Otherwise, the two compounds are identical. Both rabeprazole and lansoprazole are "asymmetrically substituted" with respect to the 4-position

[45] *Id.*
[46] *Id.* at 1357.
[47] *Id.*

on the pyridine ring because, as seen in the above representation, the substituent at the 3-position (a methyl group in both compounds) is not the same as the substituent at the 5-position (a hydrogen in both compounds). In omeprazole the pyridine ring is symmetrically substituted and has a methoxy (OCH_3) group at the 4-position.

Teva's obviousness position relied on its assertion that the skilled artisan would have chosen lansoprazole as a lead compound for further investigation.[48] In support of that position, Teva relied on evidence that "lansoprazole is twenty times superior to omeprazole for anti-ulcer action [and] has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight that would have made it desirable to a skilled artisan."[49] Teva also argued that the EP '726 reference teaches that the fluorinated substituent of lansoprazole provides "a *special path* to achieving lipophilicity."[50] However, because the fluorinated substituent would have to be dropped from lansoprazole to yield rabeprazole, the CAFC observed that "the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution."[51] On that basis, the CAFC held that the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law.[52]

In *Takeda* and *Eisai* the CAFC reiterated that prima facie obviousness of a pharmaceutical compound requires that the prior art both identify a lead compound for modification and suggest what modification should be made. The CAFC made clear that the burden on the party challenging patentability of a new chemical entity is still high after *KSR*. It is also noteworthy that the prior art in *Takeda* actually taught away from selecting and modifying compound b ("considerable increases in body weight and brown fat weight") to arrive at the invention, while in *Eisai* the very features of lansoprazole asserted to motivate its selection ("a *special path* to achieving lipophilicity") would have been lost by then modifying the compound to arrive at the claimed rabeprazole.

C. Drug Products

Of course, a patient generally doesn't simply ingest a drug substance to treat what is ailing her. Rather, that chemical compound is formulated, for example, into a tablet, a capsule, a solution, or an infusion prior to ingestion. Those types of formulations are often termed "drug

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[48] *Id.* at 1358.
[49] *Id.*
[50] *Id.* (emphasis in original).
[51] *Id.* at 1359.
[52] *Id.*

products." To develop those formulations, scientists combine a drug substance with other components, such as binders, diluents, or disintegrants, in specific proportions. Generally, those other components are known, but for purposes of this analysis, this article will assume that the specific formulation, i.e., the recipe for the formulation, is new. That raises a question in the post-*KSR* world of whether a combination of known elements along with a novel drug substance or an old drug substance, can pass muster under 35 U.S.C. § 103 even though the specific combination of those elements is new.

In *Abbott Laboratories v. Sandoz, Inc.*, the CAFC affirmed the district court's grant of a preliminary injunction barring Sandoz from selling a generic form of extended release clarithromycin pending final resolution of the case.[53] Sandoz filed an Abbreviated New Drug Application ("ANDA")[54], which the FDA approved in 2005.[55] Abbott, who markets the drug under the brand name Biaxin®XL, filed suit charging Sandoz with infringing claims 1, 4, and 6 of U.S. Patent No. 6,010,718 ("the '718 patent") and claim 2 of U.S. Patent No. 6,551,616 ("the '616 patent").[56] The '718 patent claims an extended release formulation comprising an erythromycin derivative (the derivative was not novel but was in the prior art) and a pharmaceutically acceptable polymer.[57] The claims also include functional language. In claim 1, the composition "induces statistically significantly lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability substantially equivalent to that of the immediate release composition of the erythromycin derivative."[58] In claim 4, "upon oral ingestion, maximum peak concentrations of the erythromycin derivative are lower than those produced by an immediate release pharmaceutical composition, and area under the concentration-time curve and the minimum plasma concentrations are substantially equivalent to that of the immediate release pharmaceutical composition."[59] While in claim 6, the composition has "an improved taste profile as compared to the immediate release formulation."[60] Claim 2 of the related '616 patent claims a method of

[53] 544 F.3d at 1343. The opinion of the Court was filed by Circuit Judge Newman. *Id.* at 1342. Circuit Judge Archer concurred in the judgment without writing separately Judge Archer did not join in part I of the opinion, addressing the obviousness issues discussed herein. *Id.* Although Judge Archer did not join that portion of the opinion, he certainly joined Judge Newman in affirming the injunction. *Id.* Hence, he agreed that Abbott was likely to succeed on the merits and must have felt that the claimed invention was nonobvious, although he apparently also had his own reasons for reaching that conclusion, which he did not express. *Id.* at 1371.

[54] For a definition of Abbreviated New Drug Application, see *infra* n. 148 and accompanying text.

[55] *Id.* at 1343.

[56] *Id.*

[57] *Id.* at 1344.

[58] *Id.*

[59] *Id.*

[60] *Id.*

reducing gastrointestinal side effects.[61]

The district court considered the factors relevant to the grant or denial of a preliminary injunction and found, relevant to this discussion, that Abbott was likely to prevail on Sandoz's challenges based on patent invalidity in view of the prior art.[62] In addition, the district court determined that each of the equitable factors weighed in Abbott's favor.[63]

The prior art references relied on by Sandoz were PCT Application Publication WO 95/30422 ("the '422 publication"), European Patent Application Publication No. 0,280,571 B1 ("the '571 publication"), and U.S. Patent No. 5,705,190 ("the '190 patent").[64] Sandoz argued that the asserted claims of the '718 and '616 patents would have been obvious in view of the '571 publication showing extended release formulations of erythromycin derivatives, in combination with the controlled release formulations and pharmacokinetic properties of azithromycin in the '422 publication, and the modified release alginate salt formulation of clarithromycin in the '190 patent.[65] Sandoz argued that Abbott merely "pursue[d] known options" for both the '718 and '616 patents, based on the Supreme Court's statement in *KSR:* "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."[66]

Responding, "Abbott stressed the difference between new biological compositions whose performance and effectiveness in combination cannot be confidently predicted but must be made and evaluated, and new mechanical combinations of known elements each of which predictably performs its known function in the combination."[67] Though Abbott agreed that the basic principles of pharmacokinetics were known, it argued that its choice of extended release components is not shown or suggested in the prior art to produce the pharmacokinetic properties of the subject matter recited in the claims.[68] Abbott's expert testified that "azithromycin and clarithromycin], the erythromycin derivative in Abbott's product,] exhibit different properties in four biological processes of relevance to oral drug administration: absorption, distribution, metabolism, and excretion."[69] Abbott also argued that the in vitro data provided in the prior art for scores of azithromycin formulations would not automatically correlate with

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[61] *Id.*
[62] *Id.*
[63] *Id.*
[64] *Id.* at 1345.
[65] *Id.* at 1347.
[66] *Id.* (quoting *KSR*, 550 U.S. at 421).
[67] *Id.* at 1348.
[68] *Id.*
[69] *Id.* at 1349.

pharmacokinetic parameters in vivo.[70]

On the basis of that and other evidence highlighting the unpredictability of pharmacokinetic properties resulting from inclusion of different controlled release formulations in a drug product, Judge Newman agreed with the district court's analysis that:

> the obviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in *KSR*, where the Court provided guidance that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions."[71]

On that basis the CAFC affirmed the district court's grant of a preliminary injunction.

In *In re Omeprazole Patent Litigation*, the CAFC likewise affirmed a district court's determination that a claimed formulation was nonobvious over the prior art.[72] The patents at issue were U.S. Patent Nos. 4,786,505 ("the '505 patent") and 4,853,230 ("the '230 patent"), relating to certain pharmaceutical preparations containing omeprazole, the active ingredient in Prilosec®, which inhibits gastric acid secretion.[73]

While omeprazole itself was in the prior art, the '505 and '230 patents are directed to particular novel formulations comprising omeprazole.[74] Specifically, to protect omeprazole from gastric acid in the stomach, a pharmaceutical dose may include an enteric coating surrounding the core. To counter the acidity of enteric coatings, alkaline reacting compounds ("ARCs") may be added to the drug core, but ARCs may, in turn, compromise the enteric coating by increasing its permeability to water in the stomach.[75] Indeed, an earlier formulation containing an enteric coating and drug core containing omeprazole combined with ARCs proved to have insufficient gastric acid resistance and insufficient long-term shelf life.[76]

"That task [of solving those problems] proved difficult because the two goals seemingly conflicted."[77] Increasing shelf-life required stabilizing

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[70] *Id.*
[71] *Id.* at 1351 (quoting *KSR*, 550 U.S. at 416).
[72] 536 F.3d at 1365.
[73] *Id.*
[74] *Id.* at 1365.
[75] *Id.*
[76] *Id.* at 1373.
[77] *Id.*

omeprazole in an alkaline environment; however, the acidic enteric coating would in turn be less effective at providing gastric acid resistance when in contact with that alkaline environment.[78] After many failures, the inventors attempted inserting a water-soluble subcoat, although they expected that the subcoat might prove ineffective because it would dissolve in the water that leaked through the enteric coating and would lead to degradation of omeprazole in the drug core.[79] Nonetheless, laboratory experiments surprisingly revealed that the "water-soluble subcoating increased gastric acid resistance and long-term stability" and further clinical trials confirmed that result.[80] The '505 and the '230 patents claimed such formulations.

Apotex "argue[d] that all the claims of both the '230 and '505 patents would have been obvious in light of the combination of" a prior art European patent application ("the '495 application") and "several other references."[81] The '495 application described a tablet containing omeprazole magnesium salt in a drug core with a cellulose acetate phthalate enteric coating.[82] The district court found the '495 application did not disclose tablets with a subcoating or containing an ARC. The district court further observed that the '495 application did not disclose a negative interaction between the drug core and the enteric coating, indicating that one skilled in the art would not have been looking for some structural element to insulate the drug core from the enteric coating.[83]

To overcome that shortcoming, Apotex alleged that a person of ordinary skill would understand that the cellulose phthalate enteric coating could interact with the omeprazole magnesium salt core, which is acid-labile.[84] The CAFC noted, however, that ample evidence supported both the opposite conclusion and the district court's holding.[85] Specifically, one of Astra's experts testified "that the '495 [] application does not suggest any problem relating to the interaction of the enteric coating and the drug core," and an Apotex expert agreed with Astra's expert "that the disclosure in the '495 [] application does not suggest any need to stabilize omeprazole beyond using the salt form."[86] Astra's expert also testified that "a 1985 article by Dr. Pilbrant, one of the named inventors of the '230 and '505 patents, provided further support for the view that a person of skill in the art would not have believed that an enteric coating would create a problem resulting from contact with omeprazole."[87] The CAFC thus held that,

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[78] *Id.*
[79] *Id.*
[80] *Id.*
[81] *Id.* at 1379.
[82] *Id.*
[83] *Id.* at 1379-80.
[84] *Id.* at 1380.
[85] *Id.*
[86] *Id.*
[87] *Id.*

"[b]ased on that evidence, the district court reasonably concluded that a person of ordinary skill in the art would not have seen any need to apply to Example 12 of the '495 [] application the teachings of the references disclosing subcoatings."[88]

The CAFC also upheld the district court's finding that even if a person of ordinary skill perceived the problem of interaction between the enteric coating and the drug core, it would not have been obvious to try applying a water-soluble subcoating as a means of solving that problem.[89] Agreeing with the district court, the CAFC noted that multiple different options were available should a person of ordinary skill have recognized this problem. Specifically, the CAFC noted that:

> even if one had decided to use a subcoating, one would not necessarily have used a water-soluble subcoating, since omeprazole is moisture-sensitive and needs to be delivered to the alkaline environment of the small intestine without degrading in the stomach. One of skill in the art would therefore have likely tried a non-soluble subcoating or a subcoating containing a fatty acid."[90]

Both *Abbott* and *Omeprazole* highlight how the unpredictable outcomes of combining different ingredients in pharmaceutical formulations, even where the active ingredient of the formulation is in the prior art, makes it very difficult for a challenger to prove the existence of identified predictable solutions in the prior art, which the skilled artisan would have pursued with anticipated success.

D. Cases Where the CAFC Held Claims Obvious

In both *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*,[91] and *Pfizer, Inc. v. Apotex, Inc.*,[92] the CAFC reversed district court decisions, and found the asserted claims would have been obvious and were thus invalid. These cases are noteworthy because the CAFC reversed district court findings of nonobviousness unlike *Takeda, Eisai, and Omeprazole*, where the CAFC affirmed district court findings of nonobviousness.

Pfizer, Inc. v. Apotex, Inc.[93] was decided by the CAFC just over a month before the Supreme Court's *KSR* decision. In that case, the CAFC

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[88] *Id.*
[89] *Id.*
[90] *Id.* at 1381.
[91] 499 F.3d at 1295.
[92] 480 F.3d at 1352-53.
[93] 480 F.3d 1348 (rehearing denied en banc by *Pfizer, Inc. v. Apotex, Inc.*, 488 F.3d 1377, 1378 (Fed. Cir. 2007) ("*Pfizer II*")). Three judges dissented from the Court's refusal to rehear the case en banc. *Pfizer II*, 488 F.3d at 1378.

reversed the district court's holding of validity and infringement, and held claims 1 through 3 of U.S. Patent No. 4,879,303 ("the '303 patent") invalid for obviousness. While the decision was issued before the Supreme Court's *KSR* decision, the *Pfizer* court was clearly aware that the Supreme Court was poised to review the CAFC practice of strictly applying the TSM test.

Claim 1 of the '303 patent is directed to "[t]he besylate salt of amlodipine," while claims 2 and 3 are directed, respectively, to a pharmaceutical composition and a tablet formulation comprising the besylate salt of amlodipine of claim 1.[94] "Amlodipine besylate[, or amlodipine benzene sulphonate,] is an acid addition salt form of amlodipine, formed from the reaction of amlodipine, a weak base, and benzene sulphonic acid."[95] Pfizer sells an amlodipine besylate drug product in tablet form under the tradename Norvasc®.[96]

Pfizer's scientists discovered amlodipine and its anti-hypertensive and anti-ischemic pharmacological properties before 1982.[97] Pfizer obtained U.S. Patent No. 4,572,909 ("the '909 patent"), which claims various dihydropyridine compounds and their pharmaceutically acceptable acid addition salts.[98] Moreover, the patent further discloses pharmaceutically acceptable acid addition salts of amlodipine that do not specifically include besylate, and identifies maleate, a salt formed from amlodipine and maleic acid, as the preferred salt.[99]

Later, Pfizer's scientists discovered that amlodipine maleate is chemically unstable and sticks to manufacturing equipment, leading them to identify seven alternative acids for use in forming salts of amlodipine, including besylate.[100] After finding that amlodipine besylate tablet formulations exhibited "clear superiority" in stability and in their processing characteristics, Pfizer filed a U.S. patent application directed specifically to amlodipine besylate.[101] That patent application matured into the '303 patent in suit.

During examination in the USPTO, the examiner rejected all of Pfizer's claims as obvious over the prior '909 patent, disclosing amlodipine, in view of two other prior art references: the first reference disclosed that aryl sulfonic acid salts, including besylate, of a different pharmaceutical compound, are superior to a maleate salt, which again was identified as the preferred salt form for amlodipine in the '909 patent; and the second

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[94] *Pfizer*, 480 F.3d at 1356.
[95] *Id.* at 1353 (internal footnote omitted).
[96] *Id.*
[97] *Id.*
[98] *Id.*
[99] *Id.*
[100] *Id.* at 1353-54.
[101] *Id.* at 1354-55.

reference identified the besylate form of a different pharmaceutical compound as the preferred form.[102] The examiner also cited another prior art reference, Berge, which identified 53 FDA-approved, commercially marketed anions, including besylate, that are useful for making pharmaceutically acceptable salts.[103]

To overcome the obviousness rejection in the USPTO, Pfizer filed a Rule 132 declaration by its scientist, stating that the besylate salt of amlodipine was " 'found to possess a highly desirable combination of physicochemical properties,' including good solubility, stability, non-hygroscopicity, and processability, which properties are 'unpredictable both individually and collectively.' "[104] On the basis of that declaration the USPTO allowed the '303 patent claims.

The district court followed the USPTO position and also found nonobviousness.[105] The CAFC saw the same prior art references differently and reversed the district court's holding, finding that Pfizer's claims would have been obvious.[106] An interesting question is why the CAFC came to a conclusion that differed from both the USPTO and the district court. The CAFC began by rejecting Pfizer's argument that "the '909 patent does not suggest or motivate the skilled artisan to make amlodipine besylate because" all of the anions listed in the '909 patent are non-cyclic and thus differ from besylate, which is cyclic.[107] The CAFC emphasized that a suggestion, teaching or motivation to combine the prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references.[108] Rather, the TSM may be found in other sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.[109] Specifically, the CAFC held that clear and convincing evidence established that, out of the list of fifty-three anions disclosed in Berge, a POSITA, faced with the shortcomings of the maleate tablet form, would have been motivated to use the besylate salt instead.[110] That conclusion was based on benzene sulfonic acid's known acid strength, solubility, and other known chemical properties disclosed in the prior art references. Furthermore, the CAFC reasoned that a POSITA would have known to combine that knowledge regarding benzene sulfonic acid with the teachings of the '909 patent to produce the besylate salt of amlodipine.[111]

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[102] *Id.* at 1355.
[103] *Id.*
[104] *Id.* at 1355-56 (internal quotations omitted).
[105] *Id.* at 1356.
[106] *Id.* at 1358-59.
[107] *Id.* at 1361-62.
[108] *Id.* at 1362.
[109] *Id.*
[110] *Id.* at 1363.
[111] *Id.* at 1364.

The district court had found that a POSITA would not have expected success in making amlodipine besylate. The CAFC countered, explaining that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."[112] The CAFC also rejected Pfizer's argument that it was, at most, obvious to try amlodipine in its besylate salt form. According to the CAFC, in selecting the besylate salt form, Pfizer had merely performed routine testing of salts known in the prior art. The CAFC also emphasized that the results obtained by Pfizer were predicted by the prior art.[113]

In his dissent from the CAFC's refusal to rehear the case en banc, Judge Rader criticized the original decision's focus on motivations that may have led a POSITA to experiment, stating:

> Furthermore "obvious to try" jurisprudence has a very limited application in cases of this nature. With unpredictable pharmaceutical inventions, this court more wisely employs a reasonable expectation of success analysis. In this case, salt selection is unpredictable, thus rebutting, as most other courts found, any reasonable expectation of success. Although the panel gives "lip service" to the principle that "obvious to try" does not work in this field, it nonetheless appears to be the basis for its decision in this case. In addition, the panel discerned a reasonable expectation of success by giving undue emphasis to the inventor's subjective hopes for the outcome of his experiments.[114]

Judge Rader's view of "not obvious to try" appears not to be inconsistent with the Supreme Court's "obvious to try" analysis, which presumes predictability:

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely a product not of innovation but of ordinary skill and common sense.[115]

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[112] *Id.*
[113] *Id.* at 1365-67.
[114] *Pfizer* II, 488 F.3d at 1384 (Rader, J., dissenting).
[115] *KSR*, 550 U.S. at 421.

Moreover, Judge Rader's view generally seems to have carried the day in subsequent cases, such as *Takeda*, *Eisai*, *Abbott*, and *In re Omeprazole*, discussed *supra*, where the CAFC took account of unpredictability inherent in pharmaceutical research to hold claims nonobvious.

Another post-*KSR* case where the CAFC reversed a district court and found that claims would have been obvious is *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*[116] In that case, the CAFC reversed the district court's holding of validity and infringement, and held all claims of U.S. Patent No. 5,061,722 ("the '722 patent") invalid for obviousness.

The case involved Aventis' blood pressure medication Altace®.[117] The active ingredient in Altace is ramipril.[118] Ramipril is a single stereoisomer of a chemical structure containing five stereocenters.[119] Because of those stereocenters, 2^5, (i.e, thirty-two) different stereoisomers exist in which the chemical groups present at each of the five stereocenters are arranged differently.[120] Ramipril is the stereoisomer of those thirty-two where each of the five stereocenters exists in the S form.[121] In other words, the stereoconfiguration of the stereoisomer ramipril used in Altace® is the SSSSS, or 5(S), form. Claims 1, 2, 4, and 5 of the '722 patent encompass a small genus of compounds, including the 5(S) ramipril, which is specifically claimed in claim 2.[122]

Ramipril is an angiotensin-converting enzyme inhibitor, or ACE inhibitor. Early ACE inhibitors were based on a snake venom.[123] "The active compound isolated from viper venom, known as BPP_{5a}, has six stereocenters, all of which are in the S configuration."[124] A later developed commercial product, Enalapril®, was developed before ramipril.[125] Enalapril, an SSS sterioisomer, was known to be 700 times more active than the SSR form.[126]

The structural differences between ramipril and enalapril are:

> Ramipril has the same overall structure as enalapril, with one distinction: where ramipril has two linked five-sided carbon rings (a "5,5 fused ring system"), . . . enalapril

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[116] 499 F.3d at 1294-95.
[117] *Id.* at 1294.
[118] *Id.*
[119] *Id.* at 1295.
[120] *Id.*
[121] *Id.*
[122] *Id.* at 1295-96.
[123] *Id.* at 1296.
[124] *Id.*
[125] *Id.*
[126] *Id.* at 1296-97.

> has only a single ring. The addition of the second ring gives rise to two more stereocenters than are present in enalapril; thus, ramipril has the same three stereocenters as enalapril, plus two new ones that span the fused ring system and are therefore known as "bridgehead" carbons, for a total of five as discussed above.[127]

While Aventis was working to obtain the '722 patent, Schering independently obtained a U.S. Patent No. 4,587,258 ("the '258 patent"), covering ramipril generically, without specifying particular stereoisomers.[128] As a result of an interference proceeding at the USPTO, Aventis ended up conceding priority to Schering for invention of that subject matter.[129] Nevertheless, Aventis was able to ultimately obtain its own '722 patent, claiming specifically the 5(S) form, as described *above*, and established that it was separately patentable over the lost subject matter of the interference.[130]

The prior art the CAFC focused on included various references regarding BPP_{5a}, captopril, and enalapril, prior art ACE inhibitors.[131] The CAFC observed that "all of the stereocenters in the most therapeutically active stereoisomers of these prior art compounds are in the S configuration."[132] The CAFC also considered U.S. Patent No. 5,348,944 ("the '944 patent"), which taught that, "[w]hen diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods."[133]

Finally, the CAFC relied on prior, but not publicly available, work by a Schering scientist, Dr. Smith, to synthesize SCH 31925, a mixture of 5(S) ramipril and its SSSSR stereoisomer.[134] That work was prior art under 35 U.S.C. § 102(g). Aventis argued that Dr. Smith had abandoned, suppressed, or concealed SCH 31925, but the CAFC found no error in the district court's implicit rejection of that argument, because a very similar

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[127] *Id.* at 1297.
[128] *Id.*
[129] *Id.* at 1298.
[130] *Id.*
[131] *Id.* at 1299.
[132] *Id.* at 1299 (citing *e.g.* A. A. Patchett et al., *A New Class of Angiotensin-converting Enzyme Inhibitors*, 288 Nature 280 (Nov. 20, 1980).
[133] *Id.* at 1300. Aventis challenged the prior art status of the '944 patent on appeal. Specifically, the '944 patent issued from an earlier application and was filed as a continuation-in-part of that earlier application, because it added new matter to the original disclosure. *Id.* at 1299. Aventis argued that in the interim, between developing the technique disclosed in the '944 patent and filing the continuation-in-part application, the inventors had abandoned their invention. *Id.* However, the CAFC noted that Aventis had waived this argument by failing to raise it before the district court. *Id.*
[134] *Id.* at 1300.

method had already been disclosed in an earlier patent application.[135]

The CAFC summarized that "[t]he key question is whether the 5(S) stereoisomer of ramipril, in a form substantially free of other isomers, would have been obvious over the prior art listed above to one of ordinary skill in the art at the time of the '722 patent's priority date."[136] The CAFC noted that "[t]he district court held that Lupin failed to meet its burden of proof by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to purify 5(S) ramipril into a composition substantially free of other isomers."[137] The CAFC observed that "[t]he district court saw this as a close case based principally on the absence of a clear and convincing showing of motivation," but stated that "[s]ince the date of that decision, however, the Supreme Court decided *KSR* . . . which counsels against applying the 'teaching, suggestion, or motivation' ('TSM') test as a 'rigid and mandatory formula.' "[138]

The CAFC reasoned that while it "remains necessary to show some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness, but such reasoning need not seek out precise teachings directed to the specific subject matter of the challenged claim."[139] The CAFC concluded that "[r]equiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is the active ingredient is precisely the sort of rigid application of the TSM test that was criticized in *KSR*."[140]

The CAFC then observed that, "[i]n the chemical arts, we have long held that 'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness.' "[141]

According to the CAFC:

> the "reason or motivation" need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship . . . to create an expectation," in light of the totality of the prior art, that the new compound will have "similar properties" to the

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[135] *Id.*
[136] *Id.* (internal footnotes omitted).
[137] *Id.*
[138] *Id.* at 1300-01 (quoting *KSR*, 550 U.S. at 418-19).
[139] *Id.* at 1301 (internal quotations omitted).
[140] *Id.*
[141] *Id.* at 1301 (quoting *Takeda*, 492 F.3d at 1356).

old.[142]

The Court then turned to the case before it:

> The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art. Such a purified compound is not always prima facie obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself. However, 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.[143]

The CAFC reasoned that "[o]rdinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art," and concluded that "[i]f it is known how to perform such an isolation, doing so 'is likely the product not of innovation but of ordinary skill and common sense.' "[144]

In the Court's view, the record suggested that when Dr. Smith synthesized SCH 31925, a mixture of 5(S) ramipril and its SSSSR stereoisomer, she understood that the 5(S) form of ramipril was the mixture's therapeutically active ingredient. Alternatively, the CAFC concluded:

> [e]ven if she did not, however, the prior art provides a sufficient reason to look to the 5(S) configuration. The SCH 31925 composition contained only the 5(S) and SSSSR stereoisomers of ramipril. Importantly, these forms differ by the configuration of only one carbon atom, and that atom is not one of the "bridgehead" carbons. Rather, that carbon atom is in the part of the ramipril molecule that

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[142] *Id.* (quoting *In re Dillon*, 919 F.2d at 692).
[143] *Id.*
[144] *Id.* at 1302 (quoting *KSR*, 550 U.S. at 421).

> is common to the enalapril molecule. In enalapril, as in captopril and BPP5a before it, all of the stereocenters are in the S configuration; the Merck article taught that the SSS configuration of enalapril is 700 times as potent as the SSR form. The close structural analogy between 5(S) and SSSSR ramipril and SSS and SSR enalapril would have led a person of ordinary skill to expect 5(S) and SSSSR ramipril to differ similarly in potency. Moreover, the '944 patent specifically taught that stereoisomers of ramipril "can be separated by conventional chromatographic or fractional crystallization methods." Aventis's protestations notwithstanding, there is no evidence that separating 5(S) and SSSSR ramipril was outside the capability of an ordinarily skilled artisan.145

The CAFC rejected Aventis's attempt to demonstrate unexpected results of its claimed 5(S) stereoisomer in support of nonobviousness. Specifically, Aventis relied on the district court's finding that 5(S) ramipril is eighteen times as potent as the next most potent isomer, the RRSSS form. After noting that that difference may have been unexpected, the CAFC dismissed the relevance of that fact to the issue of obviousness of the claimed invention: "The prior art supporting prima facie obviousness included the SCH 31925 mixture, and so Aventis must show that 5(S) ramipril had unexpected results not over all of its stereoisomers, but over that mixture, which did not contain the RRSSS form."[146] In other words, the CAFC wanted to see evidence comparing the claimed 5(S) against Smith's 31925 mixture of 5(S) ramipril and its SSSSR stereoisomer.

The CAFC held that "the potency of pure 5(S) ramipril is precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers. All evidence suggests, and the district court found, that potency varies with the absolute amount of the 5(S) isomer in a mixture."[147] Thus, the CAFC concluded that Aventis's claims were obvious and reversed the district court.

Aventis may be distinguishable from *Takeda* because, in *Aventis*, the obviousness issue turned on whether purifying one of only two components of a mixture to confirm that one of them was the active ingredient was obvious. Coupled with the numerous prior art references identifying all-S stereoisomers as most active, the art created what the CAFC viewed as a very predictable expectation of success, that is, the antithesis of unpredictability. In a sense, the force of the evidence supporting

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[145] *Id.* at 1302 (internal citations omitted).
[146] *Id.*
[147] *Id.*

predictability in *Aventis* that was required for the CAFC to reverse the district court, serves to highlight how difficult the burden can be on a defendant to demonstrate that a pharmaceutical invention is obvious in the context of the enormous unpredictability so prevalent in the field, as reflected by the facts in cases like *Takeda* and *Eisai*.

IV. THE IMPACT OF KSR ON PHARMACEUTICAL PATENT APPLICANTS AND PATENTEES

A. Applicants

Following *KSR*, the USPTO promulgated examination guidelines for examiners to use in evaluating obviousness. Those guidelines include seven "[e]xemplary rationales that may support a conclusion of obviousness" which can be summarized as follows:

(A) Combining prior art elements according to known methods to yield predictable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known technique to improve similar devices (methods, or product) in same way;
(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.[148]

As reflected in the guidelines, the USPTO views predictability as a key determinant of whether a claim is obvious over the prior art.

[148] U.S. Dept. Com.: U.S. Pat. & Trademark Off., *Manual of Patent Examining Procedure* vol. 2, § 2141[III], 2100-119 (8th ed. (Incorporating Revision No. 7), West 2008).

Applicants can overcome a rejection based on one of these guidelines by demonstrating the unpredictability present in the art at the time the invention was made. One way to do that is by surveying the state of the prior art and presenting that evidence to the USPTO. A declaration under 37 C.F.R. § 132 (2008), by an expert in the field, is one way to add credibility to such evidence. Working with an expert can also be valuable to identify the full scope of the relevant art and the additional aspects of uncertainty that may be overlooked by the USPTO.

If the inventors had to overcome specific hurdles to make the invention, that too can be evidence of unpredictability and a lack of anticipated success. Some of that type of evidence could be included in the patent application when it is drafted. For example, one could compare a formulation to related formulations that may not work in the same way as the claimed formulation. That type of evidence could also be discussed with the patent examiner at an interview during prosecution of the application and then presented to the Examiner in writing. In each such instance described in this and the preceding paragraph, however, care must be taken to satisfy any obligations under 37 C.F.R. § 1.56.

B. Patentees

When a pharmaceutical patentee obtains FDA approval to market its product it should list, generally within a limited time after the approval, patents that cover the approved product or uses of that product, for which "infringement could reasonably be asserted," in the FDA's "Orange Book."[149] One effect of that listing is that when an applicant for approval to market a generic copy of the product seeks FDA approval by filing an ANDA, the applicant must certify as to the patent status of the product.[150] If a patent that is not expired is listed in the Orange Book for that product, and if the generic applicant will not wait for expiration of that patent to market its product, it must make a so-called paragraph IV certification that the listed patents are invalid, not infringed, or unenforceable, and so notify the patent owner.[151] If the patent owner then sues for infringement within forty-five days of notice, market approval of the ANDA is stayed for thirty months.[152]

Patents properly listed in the Orange Book provide patentees with valuable statutory rights. Therefore, at the time of listing a patent in the Orange Book, or even in anticipation of filing of a new drug application with the FDA, patentees often evaluate the types of challenges a generic company may raise to the validity of their patent. In view of *KSR*, patentees may want to consider the basis on which the USPTO allowed the patent,

[149] 21 U.S.C. § 355(b)(1) (2000).
[150] 21 U.S.C. § 355(j)(2)(A)(vii) (2000).
[151] 21 U.S.C. § 355(j)(2)(B)(iii) (2000).
[152] 21 U.S.C. § 355(j)(5)(B)(iii) (2000).

particularly if the relevant patent was issued before *KSR* was decided. Was a rejection for alleged obviousness overcome by arguing strictly that the USPTO had failed to meet the burden of a rigid TSM test? If so, the patentee may consider whether the evidence before the USPTO supports a similar finding under the more flexible framework outlined in *KSR*. If the record of examination at the USPTO does not clearly support the nonobviousness of the claims, the patentee may wish to consider whether to file a reissue application, so additional evidence can be presented to the USPTO in support of patentability. On the other hand, the patentee may feel that she has adequate evidence that can be presented if the patent is challenged. In fact, in all the cases discussed *supra* that found nonobviousness, the patents upheld were issued before the *KSR* decision was published.

Patentees may also find it beneficial to compile evidence of unpredictability well before litigation is an issue. Often inventors have left a company during the interim between filing their patent application and the litigation over the resulting patent. However, it is often those very inventors who possess critical knowledge of the obstacles they overcame to make their invention and the uncertainty in the art regarding how to solve the problem they addressed. Cataloguing that evidence in a contemporaneous manner could provide beneficial evidence during future patent infringement litigation.

V. CONCLUSION

It is far too early to decide the impact of *KSR* on pharmaceutical patents, but the cases discussed herein give an early indication as to the present state of the law. Regardless, *KSR* has not killed pharmaceutical patents. The health of such patents will become even more evident as other decisions are issued.