Chemically Complicated: Effective Arguments to Combat "Obvious to Try" Rejections with Respect to Takeda and the Chemical Arts

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I. Introduction

Although there was initial uncertainty as to the effect the Supreme Court's decision in *KSR International v. Teleflex, Inc.* [2] would have on the obviousness analysis for chemical patents, the Court of Appeals for the Federal Circuit has largely continued to apply the traditional teaching, suggestion, motivation ("TSM") test.[3] Importantly, however, in numerous cases described in detail herein, the court has relied on the one hand, on unexpected results and, on the other hand, the "obvious to try" standard often referred to in combination in recent cases as "predictability". The court has also adopted a "lead compound" approach, wherein a certain prior art compound is identified as the closest prior art, and the claimed compound is then compared to the identified lead compound to determine whether the claimed compound would be predictable in light of the lead compound. The United States Patent and Trademark Office ("USPTO") has likewise emphasized predictability in its post-*KSR* obviousness guidelines to assist Examiners in making obviousness determinations.

This paper analyzes the post-*KSR* chemical art cases and the USPTO guidelines (both the 2007 guidelines and the 2010 updated guidelines), providing commentary and guidance for the patent practitioner in drafting and prosecuting chemical cases in the post-*KSR* era.

II. Federal Circuit Decisions

A. Case Law Review

i. Nonobvious

Takeda

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty, Ltd.*, [4]Alphapharm, a generic drug manufacturer, appealed from a district court decision holding that Takeda's patent (U.S. Patent No. 4,687,777 (the "'777 patent")) relating to the diabetes drug pioglitazone (ACTOS®) was not invalid under 35 U.S.C. § 103. Alphapharm argued that the claims of the '777 patent would have been obvious to one of skill in the art based on the closest prior art which disclosed a structurally similar compound (compound b). The structures of the relevant compounds are depicted in Table 1 below. By making two changes to the structure of compound b, replacing a methyl group with an ethyl group (homologation); and moving the ethyl group to another position on the ring ("ring-walking"), Alphapharm argued, one of skill in the art would have

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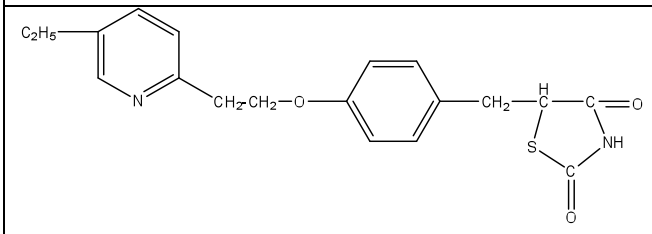
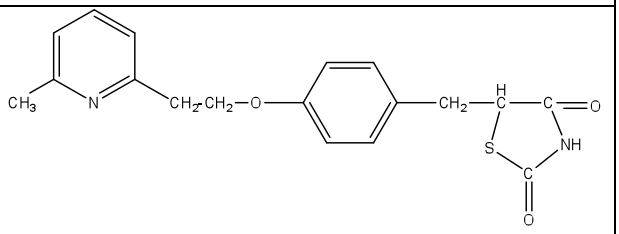
[2] 127 S. Ct. 1727 (2007).

[3] As set forth in the newly published USPTO 2010 Updated Obviousness Guidelines, "Office personnel as well as practitioners should…recognize the significant extent to which the obviousness inquiry has remained constant in the aftermath of *KSR" (Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex,* 75 Fed. Reg. 53643 (Sept. 1, 2010)).

[4] 492 F.3d 1350 (Fed Cir. 2007).

arrived at the claims of the '777 patent. Additionally, Alphapharm argued that modifying compound b to arrive at pioglitazone would have been "obvious to try" based on the prior art.

Table 1

Pioglitazone	Compound B
	

Citing *KSR*, the Federal Circuit upheld the district court's decision that the claims of the '777 patent were not invalid for obviousness under 35 U.S.C. §103. The court emphasized 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 establish *prima facie* obviousness of a new claimed compound."[5] With this in mind, the court held that one of skill in the art would not have selected compound b as the "lead compound" or starting point for developing a compound with improved properties for several reasons. First, the closest prior art disclosed "hundreds of millions" of compounds, any one of which could have been selected for modification.[6] Second, another prior art reference ("Sodha II") taught away from compound b as an antidiabetic treatment. Although an earlier Takeda patent referenced compound b as a "compound of interest", the Sodha II reference disclosed that compound b exhibited undesired properties ("considerable increases in body weight and brown fat weight") when compared with other similar compounds.[7] Thus the court held that, based on the prior art as a whole, a person of skill in the art would not have selected compound b as a lead compound for antidiabetic treatment.[8]

Additionally, Alphapharm argued that the modifications to compound b to arrive at pioglitazone would have been "obvious to try". The Federal Circuit disagreed and reasoned that this case is not one of the situations recognized in *KSR* where "there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions"[9] In this case, there were a large number of possible prior art compounds from which the skilled

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[5] *Takeda* at 1357.

[6] *Id.* at 1357.

[7] *Id.* at 1358.

[8] *Id.*

[9] *Id.* at 1359 citing *KSR,* 127 S.Ct. at 1732.

artisan could have selected for further investigation, and the prior art taught away from using compound b as a starting point for an improved antidiabetic.

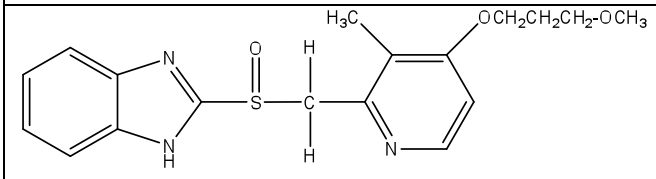
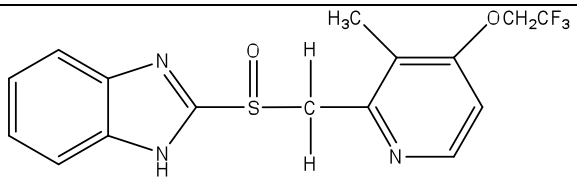
Furthermore, the court also recognized that there was nothing in the prior art to suggest making the specific modifications to compound b. Although Alphapharm argued that the claim compounds were simply homologs of compound b (and *prima facie* obvious because homologs share similar properties), the court found that there were unexpected results sufficient to rebut the *prima facie* case. While compound b was shown to be toxic, pioglitazone was shown to be non-toxic and comparatively potent. Thus, there was no reasonable expectation that pioglitazone would be shown to be non-toxic when compared to compound b.

The court found that Alphapharm did not make out a *prima facie* case of obviousness because there was insufficient evidence that compound b would have been selected as the lead compound. Furthermore, even if Alphapharm were able to make out a *prima facie* case, the court also found that it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Inc.

In *Eisai*,[10] the Federal Circuit upheld the district court's finding that the claims of the patent to rabeprazole, the active ingredient in the ulcer drug Aciphex ®, were nonobvious. Rabeprazole is a proton pump inhibitor which suppresses gastric acid production. Dr. Reddy's submitted that the claims of Eisai's patents were obvious based on prior art references that disclosed the compound lansoprazole. As shown below in Table 2, lansoprazole contains a trifluoroethoxy group at the 4–position of the pyridine ring, whereas rabeprazole has a methoxypropyl group at the corresponding position.

Table 2

Rabeprazole	Lansoprazole
	

Based on the findings of the district court and citing *KSR*, the court held that modifying lansoprazole to arrive at rabeprazole would not have been obvious to try. The court reasoned that, unlike *Takeda*, one of skill in the art would not have selected lansoprazole as the "lead compound" or starting point for developing new anti-ulcer compound because the compound already possessed the desired properties (i.e., increased lipophilicity). The court found "that

[10] *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.,* 533 F.3d 1353 (Fed. Cir. 2008).

there was no discernable reason for the skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property."[11] Thus, the court noted that "...post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."[12] Based on the evidence presented, the court found that there was no reason one of skill in the art at the time of the invention would have considered modifying lansoprazole to remove the beneficial fluorinated substituent as an "identifiable, predictable solution. As stated by the court, "[t]o the extent that an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."[13]

Sanofi-Synthelabo v. Apotex, Inc.

In *Sanofi-Synthelabo v. Apotex, Inc.*[14] the Federal Circuit also upheld the district court's holding that U.S. Patent No. 4,847,265 (the "'265 patent") was not invalid for obviousness. The '265 patent covered the thienopyridine derivative clopidogrel bisulfate (Plavix®), a drug used to prevent heart attacks and strokes. Apotex alleged that earlier Sanofi patents directed to racemic clopidogrel rendered claims to the purified dextrorotatory enantiomer obvious.

Sanofi had spent many years preparing and evaluating several thienopyridine derivates based on their knowledge that compounds of this class inhibit blood platelet aggregation. Based on their findings, Sanofi selected to pursue a compound designated as PCR 4099. The compound was, however, toxic at high doses and a racemic mixture. Although it was known in the chemical arts that separating enantiomers was difficult and not likely to provide any added benefit, Sanofi scientists attempted to separate the enantiomers of PCR 4099. After months of research, Sanofi scientists managed to find the right methods to isolate the pure dextrorotatory and levorotatory enantiomers. Upon testing of the individual enantiomers, Sanofi discovered that there was "absolute stereoselectivity". The dextrorotatory enantiomer possessed all of the beneficial antiplatelet activity without any significant neurotoxicity, while the levorotatory isomer had no antiplatelet activity but virtually all the neurotoxicity.

In this case, the court agreed with the findings of the district court that Apotex had established a *prima facie* case of obviousness based on disclosure of the racemate in Sanofi's earlier patents. However, the court found that secondary considerations ("the unpredictable and unusual properties of the dextrorotatory enantiomer and therapeutic advantages thereby provided") tipped the scale in favor of nonobviousness. The district court also found that one of skill in the art would not have predicted that the dextrorotatory enantiomer would provide all of the desired antiplatelet activity without any of the undesired toxicity. Notably, the court credited

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[11] Eisai at 1358.

[12] *Id.* at 1359.

[13] *Id.* at 1359.

[14] 550 F.3d 1075 (Fed. Cir. 2008).

evidence presented at trial that the separation was not "simple or routine", and that Sanofi had spent millions of dollars over several years developing the racemate as a therapeutic.

Apotex also alleged that the particular salt form of clopidogrel (bisulfate salt) claimed in the patent at issue was also obvious in view of Sanofi's earlier patent. However, the court found that experts from both sides agreed that it was unpredictable whether a pharmaceutically suitable crystalline salt would form from a particular acid-base combination.[15] In the court's view, factually, this case was distinguishable from *Pfizer*[16] where the court found that one of skill in the art would have narrowed the possible salts to only a few, including the claimed salt. In this case, not only were there a large number of possible salts to choose from, but the prior art taught away from using the claimed salt.[17]

Forest a pre-*KSR* decision where the court found claims directed to the antidepressant drug Lexapro®, a single enantiomer, were not obvious over the racemate because known separation techniques at the time of the invention were unpredictable and the enantiomer possessed the unexpected property of having all of the therapeutic activity and twice the potency as racemate.[18]

Proctor and Gamble Company v. Teva Pharmaceuticals USA, Inc.

In *Proctor and Gamble Company v. Teva Pharmaceuticals USA, Inc*,[19] the Federal Circuit upheld the validity of Proctor and Gamble's ("P&G") patent (U.S. Patent 5,583,122, the "'122 patent") directed to risedronate, a bisphosphonate and the active ingredient in the osteoporosis drug Actonel®. Teva argued that the claims to the '122 patent were obvious in view of an expired P&G patent that disclosed the structurally similar compound 2-pyr-EHDP. (See Table 3 below).

The court affirmed the judgment of the district court in favor of P&G, holding that, based on the finding of the lower court, a person of skill in the art would not have had a reason to make risedronate due to unpredictability in the efficacy and toxicity of bisphosphonates as class. The court, citing *Eisai* and *Takada*, concluded that the district court's finding that the invention was not obvious to a person of skill in the art was valid and supported by the evidence. While risedronate and 2-pyr EHDP are positional isomers, the prior art established that the characteristics of each bisphosphonate must be considered on its own as to its physiochemical, biological and therapeutic properties.

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[15] *Sanofi* at 1089.

[16] *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007).

[17] *Sanofi* at 1089.

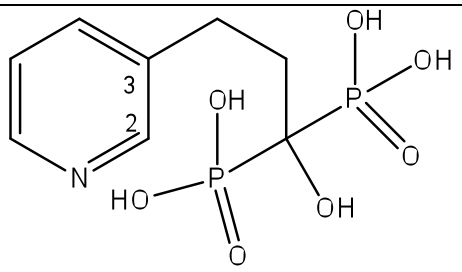
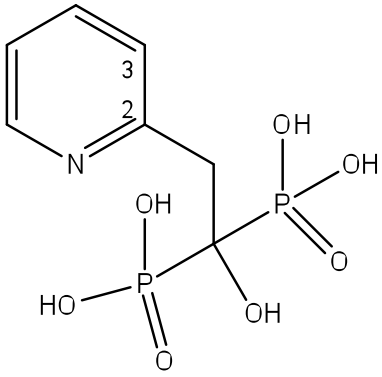
[18] *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007).

[19] 566 F.3d 989 (Fed. Cir. 2009).

The court also concluded that a person of skill in the art would not have had a reasonable expectation as to risedronate's success. The court reasoned there was insufficient support in the prior art to make the change in structure, because of the unpredictable nature of bisphosphonates. Thus, the court concluded that, with respect to *KSR*, there were no identified predictable solutions to choose from in this case.[20] Importantly, P&G showed that risedronate possessed unexpectedly improved properties (improved potency) compared to the prior art compounds.. However, P&G did not need to rely on this evidence because the court found that Teva had not established a *prima facie* case of obviousness.

Interestingly, the court also considered secondary considerations of non-obviousness in this case, finding that risedronate was commercially successful and satisfied a long-felt but unmet need for an effective osteoporosis treatment.[21]

Table 3

Risedronate	2 pyr-EHDP
	

ii. Obvious

Bayer Schering Pharma AG v. Barr Laboratories

In *Bayer v. Barr*[22], Bayer appealed the district court's finding that US Patent No. 6,787, 531 directed to a micronized form of the contraceptive drospirenone (Yasmin®) was invalid for obviousness. The parties both agreed that drospirenone was well known in the art as a contraceptive and diuretic. Additionally, drospirenone was known to be sensitive to acid (upon exposure to low pH, the compound isomerizes to form a compound that no longer possesses favorable diuretic properties). Bayer claimed that their innovation was that the micronized form

[20] *P&G* at 996.

[21] *P&G* at 998.

[22] 575 F.3d 1341 (Fed. Cir. 2009).

of drospirenone possessed increased bioavailability and the formulation did not require an enteric coating to protect against gastric acids.

At the time of the invention, micronization was a well known procedure in the art for improving the bioavailability of hydrophobic compounds. It was also known that micronizing an acid-sensitive compound may increase its sensitivity to acid. Over several years, Bayer had carried out extensive research into formulating drospirenone and found that although it was common practice to enterically coat acid-sensitive compounds, drospirenone did not require an enteric coating to be effective and could be delivered as a "normal pill."

Citing *KSR*, the court found that the claimed composition was "obvious to try" because a person of ordinary skill in the art would have had a "finite number of identified, predictable solutions".[23] Thus, in the court's opinion there were only two choices for the skilled artisan: either formulate micronized drospirenone as a normal pill or an enterically coated pill.

Aventis Pharma Deutschland GmbH v. Lupin, Ltd.

In *Aventis v. Lupin*[24], the defendant alleged that the claims directed to an isomer of high blood pressure drug ramipril (ALTACE®) in a formulation "substantially free of other isomers" was obvious. Based on studies of the racemate, known as enalapril, it was known in the prior art that the claimed isomer possessed superior potency over other isomers. Thus, the court affirmed the district court's holding that claims to the single isomer were obvious. The court stated that "if it is known that some desired 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 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."[25] In this case, the court found that since the purified isomer was expected to be more potent than the racemate, the claims were not outside of the capability of a person of skill in the art.

B. Standard for Predictability

Based on the above, it is clear that in the chemical arts, obviousness determinations made by the Federal Circuit are largely based on obvious to try and unexpected results, and hence, the issue of predictability is of paramount importance. But just how does one determine if something is predictable in the ever changing and evolving world of science? Unlike the basic mechanical invention at issue in *KSR*, the chemical arts have always been viewed as unpredictable. In fact, while the Federal Circuit found for obviousness in a majority of post-*KSR* non-chemical cases (67%), the court found non-obviousness in the majority of chemical cases

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[23] *Bayer* at 1351.

[24] 499 F.3d 1293 (Fed. Cir. 2007).

[25] *Aventis* at 1301.

(62%).[26] This trend is likely due to the inherent unpredictability in the chemical arts. As technology in the chemical arts progresses, however, what used to be unpredictable may soon become state of the art. This trend toward predictability was addressed by the Federal Circuit in a recent biotechnology-related case.[27]

In *In re Kubin*, the Federal Circuit held that claims directed to a cDNA molecule encoding a human polypeptide was obvious over the prior art which taught the isolation of the protein, a commercially available monoclonal antibody that recognized the human protein and explicit instructions for obtaining the cDNA sequence. The court stated that according to the record (from the Board of Patent Appeals and Interferences), "one of skill in this advanced art would find these claimed "results" profoundly "predictable.""[28] Furthermore, the court stated that the skilled artisan would have had every motivation to seek and every reasonable expectation of success in identifying the claimed cDNA sequence, and thus the claimed invention was "obvious to try".[29] The Federal Circuit stated that it could not, in the face of *KSR*, "cling to formalistic rules for obviousness, customize legal tests for specific scientific fields in ways that deem entire classes or prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art."[30]

It is important to note that this decision is directly counter to the holdings of the prior Federal Circuit decisions in *In re Bell*[31] and *In re Deuel*[32]. In its opinion , the court addressed *In re Deuel* and stated "[i]nsofar as *Deuel* implies the obviousness inquiry cannot consider that the combination of the claim's constituent elements was "obvious to try," the Supreme Court in *KSR* unambiguously discredited that holding. In fact, the Supreme Court expressly invoked *Deuel* as a source of the discredited "obvious to try" doctrine."[33]

The state of the art in biotechnology, as viewed by the court, has thus significantly advanced and become much more predictable in the decade following *In re Bell* and *In re Deuel*.

The "racemic mixture" cases also provide guidance as to what is predictable or obvious, with respect to claims directed to an active element of a known mixture, such as an enantiomer. In *Aventis*, the court found that the claims directed to an isomer "substantially free of other

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[26] Robert H. Resis, *Lessons to Learn from Post-KSR Pharmaceutical Obviousness Decisions*, 2 No. 2 Landslide 40 (2009).

[27] *In re Kubin,* 561 F.3d 1351 (Fed. Cir. 2009).

[28] *Id.* at 1360.

[29] *Id.* at 1361.

[30] *Id.* at 1360.

[31] 991 F.2d 781 (Fed. Cir. 1993).

[32] 51 F.3d 1552 (Fed. Cir. 1995).

[33] *Kubin* at 1358.

isomers" were obvious where it was known that the claimed isomer possessed superior potency over other isomers and separating the mixture was not outside the ordinary skill in the art. In contrast, in *Sanofi* and *Forest* the court found the claimed enantiomer was not obvious over the racemic mixture.

In particular, in *Sanofi*, the court found that the "absolute stereoselectivity" of the claimed enantiomer was unexpected and it would have been extremely difficult for one of skill in the art to separate the enantiomers from the racemate. The court went on to state that it was only with the use of improper hindsight that one would select the particular enantiomer to separate it from the racemate.

Likewise in *Forest,* the court found that the activity of the claimed enantiomer was unexpected (2x the potency of the racemate) and as in *Sanofi*, one skilled in the art would find it difficult to separate the claimed enantiomer from the racemic mixture.

Although these decisions help to clarify the predictability standard, in the real world when looking for new compounds with improved therapeutic properties, chemists look to most favorable areas for exploration, considering structure-activity relationships and trends of known compounds. Is this scientific approach inherently predictable? And if so, should the inventor chemist and/or the pharmaceutical industry be penalized for following a logical plan?

Answers to these and other questions regarding predictability are likely never to be generally answered. A case-by-case, fact driven analysis of the court's decisions in this area is thus the patent practitioners' best guide.

C. Lead Compound

Federal Circuit case law in the chemical arts has created controversy in what is referred to as the "lead compound" concept, wherein the obviousness analysis begins with the selection of a prior art compound of structural and functional similarity. Pre-*KSR*, there appeared to be a requirement that the prior art motivate one of skill in the art to identify a "lead compound" for modification before that compound could be used to establish a *prima facie* case of obviousness.[34] This requirement seemed inflexible and in tension with the way chemists operate in the pharmaceutical industry (noted above). One commentator noted that "a rigid rule that requires a person of skill to select a certain chemical compound as a "lead compound" before it can be used to establish obviousness is inconsistent with *KSR*."[35] The Federal Circuit however, has continued to use the "lead compound" approach in numerous post-*KSR* decisions.[36]

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[34] *Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000)

[35] Vincent L. Capuano, *Obviousness of Chemical Compounds: The "Lead Compound" Concept*, Intellectual Property Today July 2007, at 33 (See also Addendum, September 2007).

[36] It should be noted that the "lead compound" concept is similar to the "problem-solution" approach used in European Patent Practice when determining "inventive step."

For example, in *Takeda*, the court held 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 establish *prima facie* obviousness of a new claimed compound." [37] *Eisai* and *P&G* further demonstrate the importance of the selection of a lead compound. Taken together, these three cases appear to indicate that if the lead compound possesses undesired properties *(Takeda)*, is from an unpredictable class of compounds *(P&G)* or requires altering a substituent that already conveys the desired properties to the compound *(Eisai)*, it may be easier to establish the nonobviousness of a modified compound.

III. USPTO Post-*KSR* Guidelines

A. 2007 Guidelines

Shortly after the Supreme Court's *KSR* decision, the USPTO issued guidelines to assist Office personnel in making proper determinations of obviousness under § 103 post-*KSR*.[38] The guidelines advise Office personnel to "fulfill the critical role of factfinder" when analyzing claims for obviousness in view of the Graham factors.[39] The Graham factors are as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; (3) resolving the level of ordinary skill in the pertinent art; and (4) objective evidence relevant to obviousness or "secondary considerations", including evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results.

Once the Graham factual inquiry has been articulated by Office personnel, the guidelines outline seven rationales Office personnel may use to support a finding of obviousness. The rationales set forth in the guidelines closely track the recommendations made by the Court in *KSR*. The seven rationales are as follows:

1. Combining prior art elements according to known methods to yield predictable results;

2. Simple substitutions of one known element for another to obtain predictable results,

3. Use of known technique to improve similar devices (methods, or products), in the same way;

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[37] *Takeda* at 1357.

[38] *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co v. Teleflex, Inc.*, Fed. Reg.72 57526 (October 10, 2007*)*. **(**www.**uspto**.gov/web/offices/com/sol/notices/72fr57526.pdf**)**

[39] *Graham v. John Deere Co.,* 383 U.S. 1 (1966).

4. Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

5. "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

6. Known work in one field of endeavor may prompt variations of it for use in either the same field or a different field of endeavor based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

7. Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

It is interesting to note that each of the rationales, including "obvious to try", requires some finding of predictability (either expressly or impliedly) of the claimed invention. So in the view of the PTO, whether a claimed invention is "obvious to try" (and, therefore, obvious) turns on a determination of whether a particular solution produces unexpected/unpredictable results. This view may likely cause Office personnel to focus more on whether the claimed invention is predictable and less on whether one of skill in the art would have had a reasonable expectation of success, making the risk of the use of impermissible hindsight more likely.

According to the guidelines, rebuttal evidence for overcoming an obviousness determination may include evidence of secondary considerations and unexpected results. Therefore, it will be important to emphasize the unpredictable or unexpected nature of the inventive concept when drafting and prosecuting applications to ward off rejections under § 103. Fortunately for chemical patent practitioners, the chemical arts are deemed unpredictable and, as noted above, patents in the chemical arts are more likely to withstand scrutiny of the USPTO and the courts when challenged for invalidity based on obviousness.

B. 2010 Updated Guidelines

On September 1, 2010,[40] the USPTO issued updated guidelines to "provide additional guidance in view of decisions by the United States Court of Appeals for the Federal Circuit (Federal Circuit) since *KSR*."[41] As stated in the updated guidelines, "[a]lthough every question of obviousness must be decided on its own facts, these cases begin to clarify the contours of the obviousness inquiry after *KSR*"[42]. The guidelines go on to say that "familiar lines of argument still apply, including teaching away from the claimed invention by the prior art, lack of a

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[40] *Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex,* 75 Fed. Reg. 53643 (Sept. 1, 2010). Even though the 2010 Updated Guidelines were published at the same time this paper was being finalized, our preliminary review suggests that the guidelines confirm our analysis and conclusions.

[41] *Id.* at 53644.

[42] *Id.*

reasonable expectation of success, and unexpected results. Indeed, they may have even taken on added importance in view of the recognition in *KSR* of a variety of possible rationales".[43]

The updated guidelines provide obviousness examples from twenty-one Federal Circuit cases as "teaching points", and are divided into four general categories: Combining Prior Art Elements, Substituting One Known Element for Another, The Obvious to Try Rationale and the Consideration of Evidence. The appendix to the guidelines is attached hereto as Appendix A. All of the decisions described in detail in this paper appear in the guidelines' examples.

IV. Practical Considerations

As the USPTO 2010 Updated Guidelines make clear, the chemical patent practitioner will need to draft and prosecute applications with a keen knowledge of the post-*KSR* Federal Circuit decisions. Though not meant to be an exhaustive list of suggestions, the following are a few practical points worth noting:

- Be careful in making statements about the prior art both in the specification and during prosecution to avoid the appearance of predictability and being cornered into an adverse "lead compound".

- Provide as much evidence as possible regarding unexpected results, synergistic results and comparative data.

- Consider providing secondary indicia of nonobviousness (commercial success and long-felt unmet need).

- Be aware that certain types of claims are now more likely to be held obvious (unless there is a strong showing of unpredictability): dosage, controlled–release formulations, enantiomers, substituted elements.

V. Conclusion

Though the post-*KSR* world of obviousness in the chemical arts may not be much different from the pre-*KSR* world, the Federal Circuit and the USPTO have identified specific areas of concentration in deciding obviousness which, when taken together, may be considered as the "predictability" of a claimed invention. An emphasis on the specific facts of any given case to focus on the unpredictability of the claimed invention will thus be a necessary skill for patent practitioners in drafting, prosecuting and litigating chemical patents.

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[43] *Id.* at 53645.

Appendix A

Case	Teaching point
	Combining Prior Art Elements
In re Omeprazole Patent Litigation, 536 F.3d 1361 (Fed. Cir. 2008).	Even where a general method that could have been applied to make the claimed product was known and within the level of skill of the ordinary artisan, the claim may nevertheless be nonobvious if the problem which had suggested use of the method had been previously unknown.
Crocs, Inc. v. *U.S. Int'l Trade Comm'n.,* 598 F.3d 1294 (Fed. Cir. 2010).	A claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results.
Sundance, Inc. v. *DeMonte Fabricating Ltd.,* 550 F.3d 1356 (Fed. Cir. 2008).	A claimed invention is likely to be obvious if it is a combination of known prior art elements that would reasonably have been expected to maintain their respective properties or functions after they have been combined.
Ecolab, Inc. v. *FMC Corp.,* 569 F.3d 1335 (Fed. Cir. 2009).	A combination of known elements would have been *prima facie* obvious if an ordinarily skilled artisan would have recognized an apparent reason to combine those elements and would have known how to do so.
Wyers v. *Master Lock Co.,* No. 2009–1412, —F.3d—, 2010 WL 2901839 (Fed. Cir. July 22, 2010).	The scope of analogous art is to be construed broadly and includes references that are reasonably pertinent to the problem that the inventor was trying to solve. Common sense may be used to support a legal conclusion of obviousness so long as it is explained with sufficient reasoning.
DePuy Spine, Inc. v. *Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314 (Fed. Cir. 2009).	Predictability as discussed in *KSR* encompasses the expectation that prior art elements are capable of being combined, as well as the expectation that the combination would have worked for its intended purpose. An inference that a claimed combination would not have been obvious is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.
	Substituting One Known Element for Another
In re ICON Health & Fitness, Inc., 496 F.3d 1374 (Fed. Cir. 2007).	When determining whether a reference in a different field of endeavor may be used to support a case of obviousness (*i.e.,* is analogous), it is necessary to consider the problem to be solved.
Agrizap, Inc. v. *Woodstream Corp.,* 520 F.3d 1337 (Fed. Cir. 2008).	Analogous art is not limited to references in the field of endeavor of the invention, but also includes references that would have been recognized by those of ordinary skill in the art as useful for applicant's purpose.
Aventis Pharma Deutschland v. *Lupin, Ltd.,* 499 F.3d 1293 (Fed. Cir. 2007).	A chemical compound would have been obvious over a mixture containing that compound as well as other compounds where it was known or the skilled artisan had reason to believe that some desirable property of the mixture was derived in whole or in part from the claimed compound, and separating the claimed compound from the mixture was routine in the art.
Eisai Co. Ltd. v. *Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353 (Fed. Cir. 2008).	A claimed compound would not have been obvious where there was no reason to modify the closest prior art lead compound to obtain the claimed compound and the prior art taught that modifying the lead compound would destroy its advantageous property. Any known compound may serve as a lead compound when there is some reason for starting with that lead compound and modifying it to obtain the claimed compound.
Procter & Gamble Co. v. *Teva Pharmaceuticals USA, Inc.,* 566 F.3d 989 (Fed. Cir. 2009).	It is not necessary to select a single compound as a "lead compound" in order to support an obviousness rejection. However, where there was reason to select and modify the lead compound to obtain the claimed compound, but no reasonable expectation of success, the claimed compound would not have been obvious
Altana Pharma AG v. *Teva Pharms. USA, Inc.,* 566 F.3d 999 (Fed. Cir. 2009).	Obviousness of a chemical compound in view of its structural similarity to a prior art compound may be shown by identifying some line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound. It is not necessary for the reasoning to be explicitly found in the prior art of record, nor is it necessary for the prior art to point to only a single lead compound.

Case	Teaching point
	Obvious To Try Rationale
In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009).	A claimed polynucleotide would have been obvious over the known protein that it encodes where the skilled artisan would have had a reasonable expectation of success in deriving the claimed polynucleotide using standard biochemical techniques, and the skilled artisan would have had a reason to try to isolate the claimed polynucleotide. *KSR* applies to all technologies, rather than just the "predictable" arts.
Takeda Chem. Indus. v. *Alphapharm Pty., Ltd.,* 492 F.3d 1350 (Fed. Cir. 2007).	A claimed compound would not have been obvious where it was not obvious to try to obtain it from a broad range of compounds, any one of which could have been selected as the lead compound for further investigation, and the prior art taught away from using a particular lead compound, and there was no predictability or reasonable expectation of success in making the particular modifications necessary to transform the lead compound into the claimed compound.
Ortho-McNeil Pharmaceutical, Inc. v. *Mylan Labs, Inc.,* 520 F.3d 1358 (Fed. Cir. 2008).	Where the claimed anti-convulsant drug had been discovered somewhat serendipitously in the course of research aimed at finding a new anti-diabetic drug, it would not have been obvious to try to obtain a claimed compound where the prior art did not present a finite and easily traversed number of potential starting compounds, and there was no apparent reason for selecting a particular starting compound from among a number of unpredictable alternatives.
Bayer Schering Pharma A.G. v. *Barr Labs., Inc.,* 575 F.3d 1341 (Fed. Cir. 2009).	A claimed compound would have been obvious where it was obvious to try to obtain it from a finite and easily traversed number of options that was narrowed down from a larger set of possibilities by the prior art, and the outcome of obtaining the claimed compound was reasonably predictable.
Sanofi-Synthelabo v. *Apotex, Inc.,* 550 F.3d 1075 (Fed. Cir. 2008).	A claimed isolated stereoisomer would not have been obvious where the claimed stereoisomer exhibits unexpectedly strong therapeutic advantages over the prior art racemic mixture without the correspondingly expected toxicity, and the resulting properties of the enantiomers separated from the racemic mixture were unpredictable.
Rolls-Royce, PLC v. *United Technologies Corp.,* 603 F.3d 1325 (Fed. Cir. 2010).	An obvious to try rationale may be proper when the possible options for solving a problem were known and finite. However, if the possible options were not either known or finite, then an obvious to try rationale cannot be used to support a conclusion of obviousness.
Perfect Web Techs., Inc. v. *InfoUSA, Inc.,* 587 F.3d 1324 (Fed. Cir. 2009).	Where there were a finite number of identified, predictable solutions and there is no evidence of unexpected results, an obvious to try inquiry may properly lead to a legal conclusion of obviousness. Common sense may be used to support a legal conclusion of obviousness so long as it is explained with sufficient reasoning.
	Consideration of Evidence
PharmaStem Therapeutics, Inc. v. *ViaCell, Inc.,* 491 F.3d 1342 (Fed. Cir. 2007).	Even though all evidence must be considered in an obviousness analysis, evidence of nonobviousness may be outweighed by contradictory evidence in the record or by what is in the specification. Although a reasonable expectation of success is needed to support a case of obviousness, absolute predictability is not required.
In re Sullivan, 498 F.3d 1345 (Fed. Cir. 2007).	All evidence, including evidence rebutting a *prima facie* case of obviousness, must be considered when properly presented.
Hearing Components, Inc. v. *Shure Inc.,* 600 F.3d 1357 (Fed. Cir. 2010).	Evidence that has been properly presented in a timely manner must be considered on the record. Evidence of commercial success is pertinent where a nexus between the success of the product and the claimed invention has been demonstrated.
Asyst Techs., Inc. v. *Emtrak, Inc.,* 544 F.3d 1310 (Fed. Cir. 2008).	Evidence of secondary considerations of obviousness such as commercial success and long-felt need may be insufficient to overcome a *prima facie* case of obviousness if the *prima facie* case is strong. An argument for nonobviousness based on commercial success or long-felt need is undermined when there is a failure to link the commercial success or long-felt need to a claimed feature that distinguishes over the prior art.