Original Article

Pharmaceutical patents after *KSR*: What is not obvious?

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ABSTRACT The Supreme Court recently revisited the question of patent validity based upon obviousness in *KSR Int'l v Teleflex, Inc.* The court rejected the Federal Circuit's rigid application of the 'Teaching, Suggestion, Motivation' test in determining the obviousness of patent claims, and reasserted its precedent regarding obviousness, beginning with the seminal 1852 *HotchKiss* decision. The decision arguably makes it easier to invalidate patents for obviousness. This paper analyzes the effect of *KSR* on the state of the law concerning the obviousness of pharmaceutical and biotechnology patents in the Federal Circuit and District Courts.
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INTRODUCTION

Obviousness – in patent law – is the concept that a supposed invention is so similar to the earlier technology (the 'prior art'), albeit not identical, that it is unworthy of patent protection.[1] The application of that seemingly straightforward legal concept to various patented technologies has proven anything but obvious to the countless judges, juries, and appeals courts that have addressed it over the decades. As Judge Learned Hand noted:

> [Obviousness] is as fugitive, impalpable, wayward and vague a phantom as exists in the whole paraphernalia of legal concepts… . If there is an issue more troublesome, or more apt for litigation, we are not aware of it.[2]

Last year – after a long hiatus – the Supreme Court revisited the question of patent invalidity based upon obviousness. In *KSR Int'l v Teleflex, Inc.*[3] – a case relating to a mechanical/electrical patent for automobile

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accelerator pedals – the court arguably made it easier to prove obviousness when challenging a patent. *KSR*'s significance extends beyond mechanical patents and has directly impacted subsequent lower court decisions regarding the obviousness of pharmaceutical and biotechnology patents. That impact is the subject of this paper.

The first section of the paper reviews pre-*KSR* obviousness jurisprudence from the Supreme Court and the United States Court of Appeals for the Federal Circuit.[4] Part II discusses the *KSR* decision itself. Part III reviews post-*KSR* pharmaceutical and biotechnology obviousness decisions.

In brief summary, although the Supreme Court's *KSR* decision did relax the requirements for finding obviousness (as previously propounded by the Federal Circuit), it did not significantly depart from prior law. The lower courts' reaction to *KSR* (at least during the early period after *KSR* in 2007), however, suggested a shift against pharmaceutical and biotechnology patentees – with numerous patents being held invalid for obviousness. That initial reaction from the lower courts may be moderating in 2008.

PRE-*KSR* OBVIOUSNESS JURISPRUDENCE

The Supreme Court's classic analysis

The classic formulation for determining obviousness derives from the Supreme Court's 1966 pronouncement in *Graham v John Deere*,[5] wherein a patent covering field 'chisel plows' was held obvious in light of prior art that had similar structural features. The court explained that an obviousness analysis requires the following:

> [T]he 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.[6]

This basic test – the '*Graham* test' – has been applied to numerous and varied technologies over the past four decades. Built into the test are variable factors (eg level of ordinary skill in the art, specific history of successes, or failures in a particular technology) that allow for a flexible, case-specific application of the analysis.

Other Supreme Court cases have also given meaning and specific context to the analysis. For instance, in *United States v Adams*, 383 US 39 (1966) – 'a companion case' to *Graham* decided on the same day – the court upheld the validity of a patent relating to battery chemistry over an obviousness challenge. The court explained that Adams' battery showed unexpected and superior qualities that experts of the time had doubted were possible. Indeed, the prior art had been described as 'dangerous and inoperable'.[7] Thus, at one level *Adams* emphasises the importance of prior art that 'teaches away' from, raises doubts about, or otherwise discourages a particular technological approach.

The chemical arts: Unique, unpredictable and less likely to be obvious – Or not?

Adams is also significant at another level. As contrasted with *Graham*, *Adams* suggests that chemical patents (battery chemistry in *Adams*) may have inherent strengths when defending against obviousness challenges *vis-à-vis* mechanical patents.

In *Adams*, the patent recited a battery that used a magnesium electrode in concert with a fused cuprous chloride electrode and was activated by adding water as an electrolyte. The prior art battery used zinc and silver chloride electrodes in a different construct. It was argued that the prior art recognised that

magnesium could be substituted for zinc and cuprous chloride for silver chloride. This was rejected by the Supreme Court, which noted the superior and unexpected results of the Adams' battery, stating:

> If the use of magnesium for zinc and cuprous chloride for silver chloride were merely equivalent substitutions, it would follow that the resulting device – Adams' – would have equivalent operating characteristics. But it does not. The court below found, and the Government apparently admits, that the Adams battery 'wholly unexpectedly' has shown 'certain valuable operating advantages over other batteries' while those from which it is claimed to have been copied were long ago discarded.[8]

The decision in *Adams* is not a free pass for all chemical patentees. The *Adams* Court contrasted its holding with the earlier chemical case of *Sinclair & Carroll Co. v Interchemical Corp.*,[9] wherein a patent for a rapidly drying ink was found obvious. The *Sinclair* Court found that the patentee had merely chosen a fast-evaporating solvent for the ink from a list of known solvents with known boiling points – where the boiling point was a proxy for speed of evaporation. *Adams*, 383 US at 49–50 (quoting *Sinclair* to the effect that the patentee had merely 'select[ed] the last piece to put into the last opening in a jig-saw puzzle').

Nonetheless, *Adams* reveals that chemical patents are different. Contrast the earlier seminal case of *Hotchkiss v Greenwood*,[10] wherein the court held that a patent for clay or porcelain doorknobs – as opposed to the prior art wood or metallic doorknobs – was obvious. The *Hotchkiss* Court explained that the substitution of one material for another – even if producing a superior or cheaper product – in the context of a mechanical object cannot support a patent, stating:

> But this, of itself, can never be the subject of a patent. No one will pretend that a machine made, in whole or in part, of materials better adapted to the purpose for which it is used than the materials of which the old one is constructed, and for that reason better and cheaper, can be distinguished from the old one; or, in the sense of the patent law, can entitle the manufacturer to a patent.[11]

What distinguishes the substitutions in *Adams* (eg magnesium for zinc and cuprous chloride for silver chloride) from those in *Hotchkiss* (clay or porcelain for wood or metal)?

At some very basic level, it is the complexity and unpredictability of battery chemistry as compared with the mundane nature of doorknobs. One simply senses that 'doorknob technology' is hardly a technology at all. Supreme Court Justices and other federal judges and juries knew that one could make a doorknob out of clay or ceramic – they 'expected success'. By contrast, they knew nothing about the likelihood of success of water-activated magnesium/cuprous chloride batteries.

Similarly, in *Reckendorfer v Faber*,[12] the court found obvious a patent directed to a lead pencil combined with an india-rubber eraser. The court contrasted this 'pencil combination' with an inventive chemical combination of sulphur and rubber (vulcanisation) that produced unique and unexpected results, stating:

> The combination consists only of the application of a piece of rubber to one end of the same piece of wood which makes a lead-pencil… . Each, however, continues to perform its own duty, and nothing else. No effect is produced, no result follows, from the joint use of the two….
> *The combination, to be patentable, must produce a different force or effect, or result in combined forces or processes, from that given by their separate parts. There must be a new result produced by their union: if not so it is only an aggregation of separate elements. An instance and an illustration are found in the discovery, that, by the use of sulphur mixed with india rubber, the rubber could be vulcanized, and that without this agent the*

> *rubber could not be vulcanized. The combination of the two produced a result or article entirely different from that before in use.*[13]

Chemistry – with its infinitesimal atoms and unpredictable interactions and transformations – affords greater mystery than simple mechanical combinations. Courts have routinely characterised chemistry as an unpredictable science.[14] With respect to obviousness, the Supreme Court explicitly noted in *Great Atlantic & Pacific Tea Co. v Supermarket Equip. Corp.*[15] that chemical combinations are generally different from mechanical ones, stating:

> The conjunction or concert of known elements must contribute something; only when the whole in some way exceeds the sum of its parts is the accumulation of old devices patentable. *Elements may, of course, especially in chemistry or electronics, take on some new quality or function from being brought into concert, but this is not a usual result of uniting elements old in mechanics.*

The Federal Circuit's pre-*KSR* 'Teaching, Suggestion, Motivation' test

The United States Federal Circuit Court of Appeals (the 'Federal Circuit') is the exclusive venue for appeals from all US District Court decisions involving patent matters.[16] Federal Circuit decisions can be appealed to the US Supreme Court – if the High Court chooses to entertain the appeal.

Prior to *KSR*, the Federal Circuit had crafted a rule known as the'Teaching, Suggestion or Motivation' test (the 'TSM' test) that it applied to obviousness determinations. This test *required*, for obviousness to be found, that the allegedly invalidating prior art references have taught, suggested, or motivated combining the older elements to make the new invention. For example, in *Brown & Williamson Tobacco Corp. v Philip Morris Inc.*,[17] the Federal Circuit explained that, 'a showing of a suggestion, teaching or motivation to combine is "an essential evidentiary component of an obviousness holding"'.

As a result of the TSM test, patents that might otherwise have seemed obvious could be upheld where the prior art did not appear to have an explicit statement (teaching or suggestion or motivation) that pointed in the exacting direction of the invention in the patent. The rationale for such a test was to avoid hindsight reconstruction of the patented invention, having that invention in mind.

The Federal Circuit used this TSM principle in *Teleflex, Inc. v KSR Int'l Co.*[18] to reverse the District Court's holding that a patent entitled 'Adjustable Pedal Assembly with Electronic Throttle Control' was obvious. The patent at issue was directed to an automobile accelerator pedal that was *both* adjustable to the driver and also electronically controlled the throttle (via a monitor of pedal pivot that conveyed that information electronically to the throttle of the engine). The District Court found obviousness (on summary judgment, without the need for a trial) based upon a prior art patent (the 'Asano patent') that disclosed 'all of the structural limitations of the adjustable pedal without the electronic controls'.[19] The District Court reasoned that electronic throttle controls were known and would have been readily seen to be usable with the adjustable pedal of Asano.

By contrast, the Federal Circuit held that a finding of obviousness was not necessarily warranted and further inquiry was needed to determine whether the prior art truly motivated such a combination. The Federal Circuit explained, 'we have consistently held that a person of ordinary skill in the art must not only have had some motivation to combine the prior art teachings, but some motivation to combine the prior art teachings in the particular manner claimed'.[20] Thus, for the Federal Circuit, the TSM test required greater proof before obviousness could be found.

THE SUPREME COURT'S *KSR* DECISION

The Supreme Court took up the case and, in *KSR Int'l Co. v Teleflex Inc.*,[21] reversed the Federal Circuit, holding that the 'Adjustable Pedal Assembly with Electronic Throttle Control' patent was obvious without further inquiry. The court noted that both electronic accelerator pedals and adjustable pedals were known in the prior art. It further noted that the 'prior art contained patents involving the placement of [electronic] sensors on adjustable pedals as well'.[22]

The un-doing of the 'TSM Test'

With that backdrop, the court proceeded to examine the TSM test. Rejecting a 'rigid' application of the test, the court stated:

> When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court … captured a helpful insight…. *As is clear from cases such as Adams, [a chemical case] a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art*… .This is so because invention in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. *Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation*, or by overemphasis on the importance of published articles and the explicit content of issued patents….
>
> There is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.[23]

Thus, the court held that while the *presence* in the prior art of a 'teaching, suggestion or motivation' to combine old elements certainly can be evidence of obviousness, the *absence* of an explicit 'teaching, suggestion or motivation' does not preclude obviousness – although, as in the past, there must be some reason for the combination. The reason, however, can derive from common sense itself.[24]

'Obvious-to-Try' may be obvious

The *KSR* Court also stated that an approach that would be 'obvious-to-try' '*might*' be obvious if one would predict success:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'…. *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 a good reason to pursue the know options with his or her technical grasp. If this leads to the *anticipated success*, it is likely the product is not of innovation but of ordinary skill and common sense. *In that instance the fact that a combination was obvious to try might show that it was obvious under § 103*.[25]

This passage initially produced comment that the 'old law' that 'obvious-to-try is not obvious' had been eviscerated.[26] The 'old law' itself, however, recognised that in appropriate circumstances something that was *both* obvious-to-try and reasonably expected to succeed could be obvious. As the Federal Circuit said in *In re O'Farrell*:

> It is true that this court and its predecessors have repeatedly emphasized that 'obvious to try' is not the standard under § 103. However, the meaning of this maxim is sometimes lost. *Any invention that would in fact have been obvious under § 103 would*

> *also have been, in a sense, obvious to try*. The question is: when is an invention that was obvious to try nevertheless nonobvious?… Obviousness does not require absolute predictability of success… . *For obviousness under § 103, all that is required is a reasonable expectation of success*.[27]

Thus, again in this respect, the Supreme Court's *KSR* decision was not as radical as first thought. Predictability remains the key to an obviousness determination.

It is also interesting to note the Supreme Court's emphasis on 'design need or market pressure' which sounds something like a 'suggestion, teaching or motivation', although it was probably not intended to be a 'rigid' requirement.

The person of 'Ordinary Creativity'

Among the *Graham* factors to be considered in an obviousness determination is the 'level of ordinary skill in the pertinent art'. Traditionally, patentees argue for a low level of knowledge and creativity (people who would not think an invention is obvious) and those challenging patents argue for a higher level.

The Federal Circuit has tended to view the 'person of ordinary skill' as quite ordinary. For instance, in *Standard Oil Co. v American Cyanamid Co.*, the Federal Circuit stated:

> *A person of ordinary skill in the art is also 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.[28]

By contrast, the *KSR* Court noted that a 'person of ordinary skill is also *a person of ordinary creativity*, not an automaton'.[29] This view would appear to favour those challenging patents. Creative people – even those with 'ordinary creativity' – theoretically should be more likely to view differences from the prior art as minor or trivial and hence obvious.

The practical consequence of all this for real-world patent litigation remains to be seen. Although litigation over obviousness often includes battles over how much education, knowledge, intelligence, and creativity 'one of ordinary skill in the field' has – with patentees arguing for less and defendants arguing for more – years of litigation leave one with the sense that, ultimately, judges and juries struggle to view the technology through the eyes of a hypothetical 'person of ordinary skill' and more often view it through their own mind's eye.

The passage of time, the growth of knowledge, and the need for a flash of genius?

In its concluding passages, the *KSR* Court observed philosophically – perhaps poetically – that:

> We build and create by bringing to the tangible and palpable reality around us new works based on *instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more*. And as progress beginning from higher levels of achievement is expected in the normal course, *the results of ordinary innovation are not the subject of exclusive rights under the patent laws*. See US Const. Art. I, § 8, cl. 8. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in § 103. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.[30]

While this concept is not entirely new in the law or in science – Einstein once famously remarked that his work 'stood on the shoulders of giants' like Newton – *KSR*'s statement has some interesting implications.

First, the concept that the 'threshold is always being raised' allows once unpredictable arts (like chemistry and biotechnology) to

mature to stages where much of the technology could be viewed as obvious.

Secondly, *KSR*'s statement that 'ordinary innovation' is not good enough raises the spectre of the old 'flash of genius' requirement for patentability. In *Cuno Eng'g Corp. v Automatic Devices Corp.*,[31] the court had stated that: 'the new device, however useful it may be, must reveal the flash of creative genius, not merely the skill of the calling [to be patentable]'.

This 'genius' law, however – in its most extreme sense – had been effectively set aside. Section 103 of the Patent Code states: 'Patentability shall not be negatived by the manner in which the invention was made'. Furthermore, the Federal Circuit noted in *Jones v Hardy*[32] that 'the requirement for a "flash of genius" … was in disregard of the [Supreme] Court's description of that phrase as a mere "rhetorical embellishment" in *Graham*, *supra*, 383 US at 15, note 7'.

Whether *KSR* has resurrected the 'flash of genius' requirement remains to be seen.

POST-*KSR* PHARMACEUTICAL-BIOTECHNOLOGY CASES

In 2007, it certainly felt like the 'flash of genius' requirement had been resurrected in pharmaceutical and biotechnology patent litigation in the lower courts. Numerous patents, with rare exception, were found obvious. That trend seems to be moderating in 2008. We review examples below.

The Federal Circuit in 2007

Pfizer v Apotex – *Salts*

The 2007 assault began just *before KSR* was decided.

Perhaps anticipating *KSR* and trying to head it off, the Federal Circuit decided *Pfizer v Apotex*,[33] – finding obvious the patent for a new salt of amlodipine (the high blood pressure medication Norvasc®). The salt counter-ion was besylate (benzene sulphonic acid anion) – a rarely used counter-ion that had never been used with amlodipine. It was one of 53 possible salts. Furthermore, amlodipine besylate was found to have unexpected formulation benefits, including improved stickiness that helped with tabletting.

The logic of the *Pfizer v Apotex* decision was reminiscent of that set forth *Sinclair & Carroll Co. v Interchemical Corp.*,[34] wherein the choice of a solvent for a 'rapidly-drying ink' from a short list of solvents with known evaporation properties was deemed obvious. The Federal Circuit opined that this case involved the mere selection of a salt from known possibilities. Of course, the *Pfizer* case involved much more than simple boiling points for ink solvent – pharmaceutics, organic chemistry, and physiology, with all their unpredictable interplay, were involved.

A rehearing *en banc* was sought and was denied. The dissenting Federal Circuit judges urged that the decision ignored the unexpected and unpredictable beneficial properties of the particular salt chosen and that prior law had deemed such properties to be a basis for non-obviousness.[35] Unique formulation and stability properties have certainly served to sustain pharmaceutical patents in the past.[36]

Beyond the rarity of this particular counter-ion and its unexpected formulation properties, there is also the general unpredictability of any chemical combination when used in the body. Furthermore, although not discussed in the opinion, the combination of two chemicals can produce unexpected interactions and chemical instability. Such problems, if present, would teach away from using besylate in combination with amlodipine.[37]

Nonetheless, the patent was invalidated.

Daiichi Sankyo v Apotex – *'Similar' compounds and their uses*

In *Daiichi Sankyo Co. v Apotex, Inc.*,[38] a method-of-treatment patent covering the novel use of the antibiotic ofloxacin to topically treat bacterial ear infections was

found obvious. The prior art had used a different antibiotic – a different molecule – called ciprofloxacin to treat ear infections.

The Federal Circuit first stated that ofloxacin and ciprofloxacin are similar molecules from the same general class of antibiotics known as fluoroquinolones. Also, in a rare case where the knowledge of the 'person of ordinary skill' was at issue, the Federal Circuit found error in the lower court's assessment of 'one of ordinary skill' and held that those of skill in this area were not merely general physicians, but specialists in drug and ear treatments.

The concern in the field was that topical administration of drugs inside the ear can produce ototoxicity – otherwise known as ear and hearing damage. Although ciprofloxacin may have been safe, that hardly provided proof that ofloxacin was. 'Similar' molecules can produce very different results within the body. As the Nobel Prize winning chemist Roald Hoffman has said:

> A few atoms added here, subtracted there, is all it takes to make the difference between male and female sex characteristics, between a harmless molecule and a deadly addictive one….[39]

Consider the single atom difference between carbon dioxide and carbon monoxide – and the resultant deadly nature of carbon monoxide. Ethanol (drinking alcohol) has one more carbon than methanol, yet methanol can cause blindness. Thalidomide is a mixture of mirror-image isomers, where one isomer is believed to cause horrific birth defects. Small chemical differences can have large physiological effects.

The *Daiichi* Court's point appears to be that testing ofloxacin for ototoxicity was routine.[40] This leaves us with the question of whether 'routine' testing – even where it results in a new and previously unknown invention – is ever sufficient to support a patent. Is a 'flash of genius' required after all? Would the 'routine' study of different light bulb filaments by Edison have survived this scrutiny?

Aventis v Lupin – *Stereoisomer mixtures*

In *Aventis Pharma Deutschland GMBH v Lupin, Ltd*,[41] the Federal Circuit found a patent covering a particular stereoisomer[42] used for treating high blood pressure (the ACE inhibitor Ramipril®) to be obvious.

The patented compound was one of 32 possible isomers – having all of its five chiral centres in the 'S' configuration. The prior art was deemed to include a mixture of the particular compound of interest (SSSSS) with its stereoisomer (SSSSR).[43] The court then reasoned that:

> Such a purified mixture is not always prima facie obvious over a mixture … [However,] [o]rdinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture … . If it is known how to perform such an isolation, doing so 'is likely the product not of innovation but of ordinary skill and common sense.' *KSR*, 127 S. Ct. at 1742.[44]

The court went on to discount evidence of an unexpected 18-fold increased potency over the 'RRSSS' stereoisomer, stating that it involved a comparison with the wrong prior art.

The Federal Circuit also buttressed its argument by noting that the prior art also included a 'similar' compound called Enalapril® which – although a different molecular structure – had three chiral centres that were all in the 'S' configuration.

Ramipril®, with five chiral carbons, has 32 possible stereoisomers. There would seem to be no clear reason, without prior knowledge of the invention itself, why the two additional chiral carbons in Ramipril® should be in the 'S' configuration, even though the three chiral carbons in Enalapril® were in the 'S' configuration. The 'S' and 'R' nomenclature has no particular correlation to physiological activity – and need not extrapolate from one molecule to another, let alone from one set of chiral carbons on one molecule to different chiral carbons on another molecule.

That said, the Federal Circuit found the mixture of SSSSS with SSSSR to be the primary prior art reference and held the patent invalid.

Forest Labs v Ivax Pharmaceuticals – *Enantiomers and racemic mixtures*

In contrast with *Aventis*, the Federal Circuit upheld a patent on an enantiomer (sold as the anti-depressant Lexapro®) in *Forest Labs v Ivax Pharmaceuticals*.[45] Despite prior art disclosing the racemic mixture, the court stated:

> Forest argues that any prima facie obviousness based on racemic citalopram was rebutted by the evidence demonstrating the difficulty of separating the enantiomers and the unexpected properties of the (+) citalopram. Forest argues that it was unexpected that all the therapeutic benefit of citalopram would reside in the (+) enantiomer, resulting in escitalopram having twice the potency of racemic citalopram… . We agree with Forest.[46]

In affirming the District Court's refusal to find obviousness, the Federal Circuit stated that the patentee's case was buttressed by evidence of 'the failure of the inventors and others to resolve [separate] citalopram without undue experimentation'.[47] Apparently, the separation of the two enantiomers involved complex chemical manipulations that were uncertain to succeed. In a nutshell, the patentees were able to recite a powerful story of invention.

Pharmastem Therapeutics v Viacell – *Stem cells*

In *Pharmastem Therapeutics, Inc. v Viacell, Inc.*,[48] the Federal Circuit invalidated a patent for compositions and methods of using cryopreserved umbilical-cord stem cells to reconstitute adult human blood and immune cells. In part, the Federal Circuit reasoned that the patent itself conceded the existence of these types of stem cells in the prior art.[49] Despite noting that the inventors 'may have significantly advanced' the art, the court concluded that the 'inventors merely used routine research methods to prove what was already believed to be the case'.[50]

By contrast, the dissent noted that:

> The undisputed evidence at trial was that these long-sought life-saving inventions were achieved amid general scientific skepticism, despite the extensive research that was being conducted by many scientists in this field, as set forth in the patents in suit. The discoveries of these inventors were met with universal acclaim and widespread utilization, including the founding of many commercial enterprises, all of which are reported to have licensed the patents except for these defendants. Unimpressed by these considerations, my colleagues on this panel now reconstruct these inventions by selection and inference, with perfect hindsight of the discoveries.[51]

In re Omeprazole Patent Litigation – *Formulation changes*

In *In re Omeprazole Patent Litigation*,[52] the Federal Circuit found a patent for creating a particular formulation of omeprazole (Prilosec®) via an *in situ* reaction to be both inherently anticipated and also obvious. The obviousness finding as to one claim was based upon the substitution of one 'alkaline reacting compound' for another known 'alkaline reacting compound' in one of the original tablet layers.

Omeprazole is a gastric-acid inhibitor that is chemically unstable in the presence of acidity. Thus, it needs to be encapsulated in protective coatings as it passes through the human stomach, which is acidic. The patent here was directed to a process for preparing a three-layer tablet from two initial layers by an *in-situ* reaction between chemicals in those two layers. This seemingly elegant solution to protecting the actual medicine in the inner core from chemical breakdown was found obvious based upon the substitutability of one type of alkaline reactive chemical in the prior art for another that was part of the patented process.

Although specific to its own facts, the case may be indicative of a trend against formulation type patents. Such patents, however, can often provide key advances that benefit patients by allowing for new modes of drug administration and stable shelf life.

Takeda Chemical v Alphapharm – *New molecule*

In *Takeda Chemical Indus. v Alphapharm Pty.*,[53] the court upheld a patent on an anti-diabetic compound, stating:

> [The] test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.....Thus, 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.[54]

The obviousness argument rejected in *Takeda* was based upon a multi-step chemical modification of the prior art. First, a so-called 'compound b' from the prior art needed to be selected as the 'lead compound' – or compound upon which further modifications would be made. Next, 'compound b' needed to have one of its methyl groups changed into an ethyl group; then the ethyl group needed to be moved around on a ring structure from the '6-position' to the '5-position'.[55]

The District Court and the Federal Circuit rejected the obviousness argument pointing out that 'compound b' was one of 'hundreds of millions' of possible compounds disclosed in the prior art – hence rejecting the proposition that 'compound b' would have been considered a lead compound at all by those of skill in the art.[56] Furthermore, even if 'compound b' were considered as a lead compound, the court rejected the view that the very specific molecular changes required would have been obvious or suggested by the prior art.[57]

The District Courts in 2007

Altana v Teva – *New molecule*

In *Altana Pharma AG v Teva*,[58] the District Court, relying on *KSR*, refused to issue a preliminary injunction against an accused infringer because it concluded that the patentee was unlikely to succeed on the merits – because of obviousness. The patent was directed to a new chemical entity known commercially as Protonix® (a stomach acid 'proton pump' inhibitor).

The court's preliminary assessment of obviousness employed a multi-step logic: (1) the prior art was said to have the same 'chemical backbone', (2) there was a desire in the art to have molecules with lower *p*Ka values, and (3) the art allegedly knew that methoxy substitutions produced lower *p*Ka values.

Given the perhaps infinite substitutions that one might make to any particular chemical backbone, one could ask whether this logic constitutes the 'identification of a reason to modify a known compound' that the *Takeda* Court spoke of? Or is this hindsight reconstruction?

Novartis v Teva – *Pro-drugs*

In *Novartis v Teva*,[59] the District Court refused a preliminary injunction on the ground that the patent was likely to be found obvious. The patent was directed to a herpes drug called famciclovir which is converted into penciclovir in the body. Penciclovir was one of five nucleosides known to have effectiveness against herpes and low toxicity.

The court reasoned that the prior art knew that penciclovir belonged to a group of nucleoside drugs that were effective antiviral agents. The prior art also supposedly knew that penciclovir was potentially toxic and also not well absorbed when taken orally. The court also reasoned that 'making a pro-drug was not new technology' and that pro-drugs of other nucleosides were known.[60] Thus, the court concluded that penciclovir was an

obvious 'lead compound' and that the specific ester modifications that were made to penciclovir were obvious.[61]

This analysis was taken despite the fact that other companies had abandoned their studies of penciclovir, despite the numerous other possible chemical modifications that might have been made, and despite arguments for unexpected advantages for famciclovir.

McNeil v Perrigo and Ortho-McNeil v Kali – *Combinations*

In *McNeill-PPC v Perrigo*,[62] the District Court found a patent for a combination of famotidine (a stomach acid inhibitor) and aluminium or magnesium hydroxide (antacids) contained within an impermeable coating to be obvious. The court concluded that the prior art disclosed the same types of combinations and also separately taught the use of impermeable coatings to mask medicinal tastes. Famotidine was known to have a bitter taste. The patentees urged that there were several other ways to deal with the bitter taste (including sweeteners) and one of ordinary skill would not have been motivated to use impermeable coatings. The court rejected this, noting prior use of coatings with famotidine alone, and found the choice obvious.

In *Ortho-McNeill Pharmaceutical, Inc. v Kali Labs.*,[63] the District Court found a patent directed to a specific weight ratio of the pain medicines tramadol and acetaminophen to be obvious, where the prior art had presented the combination in a weight ratio that was different from the patented ratio by a two-fold factor (a 1:10 ratio in the prior art *v* a 1:5 ratio in the patent). In addition to the one prior art reference that had a 1:10 weight ratio for the combination, the court also reviewed prior art that suggested combinations of the two drugs and also discussed dosages for each drug separately. Calculating ratios for a combination based upon dosages expressed for the medicines taken separately, the court determined that the move from 1:10 to 1:5 was obvious.

Moderation in 2008?

Esai v Dr Reddy's – *New molecule*

In *Esai Co. v Dr Reddy's Labs., Inc.*,[64] the Federal Circuit upheld the validity of a patent directed to a new chemical entity called rabeprozole (a stomach proton-pump inhibitor). As in *Takeda*, and in contrast to *Altana*, the Federal Circuit observed (1) that *KSR* still requires that there be a reason to alter existing molecules and (2) that unpredictability in the chemical arts tends against finding obviousness, stating:

> Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (ie a lead compound) in a particular way to achieve the claimed compound… .
> To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified, predictable solutions' may present a hurdle because potential solutions are less likely to be genuinely predictable.[65]

The obviousness argument that was rejected in *Esai* was based upon prior art references which disclosed allegedly similar chemical structures and a reference article entitled 'Activity Relationships of Substituted Benzimidazoles'. The patented compound (rabeprazole) differed from one of the prior art compounds (lansoprazole) only in lacking a fluorinated substituent (a trifluoro-ethoxy group present on lansoprazole). Nonetheless, the court questioned whether lansoprazole should be considered a 'lead compound' in the first place. Furthermore, the court noted the absence of a clear chemical modification that would predictably solve the problem of gastric-acid secretion. Indeed, the court noted that the trifluoro-ethoxy substituent might be viewed as a desirable (lipophilic) chemical constituent that one would not want to remove – a teaching away.

With these observations in mind, the Federal Circuit affirmed the District Court's refusal to find obviousness.

Ortho-McNeil v Mylan – *New molecule*

In *Ortho-McNeil Pharmaceutical, Inc. v Mylan Labs.*,[66] the Federal Circuit also upheld as non-obvious a patent covering an new chemical entity for the treatment of epilepsy known as topiramate and sold as Topomax®. This molecule had been discovered as an intermediate compound during the search for an anti-diabetes medicine.

The Federal Circuit stated that the arguments for obviousness constituted nothing more than hindsight reconstruction of the invention. The court noted that *KSR*'s comments about a 'finite number of identified predictable solutions' did not apply where an inventor happened upon a compound among countless other possible compounds while researching a completely different problem (diabetes as opposed to epilepsy). The court also noted 'powerful unexpected results', 'skepticism of experts', 'copying', and 'commercial success' as objective indicia of non-obviousness.[67]

Finally, the court commented on the 'flexible' TSM test (after *KSR*), stating:

> As this court has explained … a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case… .[68]

What accounts for 2008's moderation? Because of the fact-specific nature of these cases, it is hard to say with certainty. It may be, however, that the lower courts have had time to reflect on the less-than-radical nature of the Supreme Court's *KSR* decision and are starting to accept – as the Supreme Court did – the need for a bulwark against hindsight reconstruction of inventions in obviousness cases. It may also be that litigants that had previously been over-confident when defending against obviousness allegations are now marshalling every last bit of factual and legal argument at their disposal. It is fair to say that patentees in court and applicants in the Patent Office should be prepared, at a minimum, to lay out in chapter and verse the reasons why their chemical and biotechnology inventions are different and have unexpected and unpredictable qualities from the prior art. Furthermore, it seems fair to say that 'new chemical entity' patents (setting the District Court decision in *Altana* aside) are displaying somewhat greater vitality in the face of obviousness challenges *vis-à-vis* other types of pharmaceutical patents after *KSR*.

CONCLUSION

The patent system is designed to promote innovation by rewarding risky investment in uncertain research. As Adam Smith explained long ago:

> When a company of merchants undertake at their own risk and expence [sic], to establish a new trade with some remote and barbarous nation, it may not be unreasonable … to grant them, in case of their success, a monopoly of the trade for a certain number of years. It is the easiest and most natural way in which the state can recompense them for hazarding a dangerous and expensive experiment, of which the public is afterwards to reap the benefit. A temporary monopoly of this kind may be vindicated upon the same principles upon which a like monopoly of a new machine is granted to its inventor, and that of a new book to its author… .[69]

The innovative pharmaceutical and biotechnology industries fit well into the model described by Smith. Hundreds of millions of dollars, even billions, are invested to bring even a single medicine to fruition. Efforts often fail along the way. In the absence of a strong patent system, it is hard, if not impossible, to encourage that initial effort and investment.

And the public certainly does benefit from those efforts. From 1900 to 2000, average life expectancy in the US increased from 47 to 77

years.[70] The development of new treatments for old plagues on humanity certainly accounts for some, if not a large part, of that increase.

Trends in patent law are hard to identify because of the fact-specific nature of each case. Obviousness, in particular, can turn on detailed, case-specific nuances. Nonetheless, at the risk of generalising, it seems fair to say that the legal environment appears to have turned against patentees, for the moment. Beyond obviousness, it has become, in general, easier to get into court to challenge patents,[71] harder for patentees to prove infringement,[72] obtain injunctions,[73] and obtain findings of wilful infringement.[74] Congress and the Patent Office are also seeking to tighten rules about patents and arguably limit patent rights.

Undeniably, there are some patents that do not represent true invention and should not issue; when issued they hinder, rather than advance, technology. Defining the line where 'invention' begins, however, is – as Learned Hand noted – like defining the contours of a phantom. Sometimes even seemingly small advances are of great value.

Churchill once said that 'The empires of the future are the empires of the mind'.[75] In an age when we are searching for cures for the diseases of an ever-aging and expanding population as well as technological answers for global warming and energy demand, it is fair to ask whether the latest developments in the patent law are helpful or harmful to the protection and encouragement of those future 'empires of the mind'.

REFERENCES AND NOTES

1. See 35 U.S.C. § 103, wherein it is stated: 'A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made'.

   Beyond this statutory basis, the Supreme Court has suggested, if not stated outright, that the Constitution itself requires that inventions be non-obvious to be patentable. See *Sakraida v AG Pro, Inc.*, 425 US 273, 279 (1976) ('It has long been clear that the Constitution requires that there be some "invention" to be entitled to patent protection'.); *Anderson's-Black Rock, Inc. v Pavement Salvage Co.*, 396 US 57, 61 (1969) ('The patent standard is basically constitutional. Article I, § 8, of the Constitution authorizing Congress "[T]o promote the Progress of ⋆ ⋆ ⋆ useful Arts" by allowing inventors monopolies for limited times. We stated in *Graham v John Deere Co.*, 383 US 1 … that under that power Congress may not "enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby". Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must "promote the Progress of ⋆ ⋆ ⋆ useful Arts". This is the *standard* expressed in the Constitution and it may not be ignored'.); cf. *KSR Int'l v Teleflex, Inc.*, 127 S. Ct. 1727, 1746 (2007) ('See US Const. Art. I, § 8, cl. 8. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in § 103'.).
2. *Harries v Air King Prods. Co.*, 183 F.2d 158, 162 (2d Cir. 1950).
3. 127 S. Ct. 1727 (2007).
4. The United States Court of Appeals for the Federal Circuit (the 'Federal Circuit') is the *only* court that can hear appeals from final District Court (federal trial court) decisions in patent cases. 28 U.S.C. § 1295(a)(1). It also hears appeals from the Patent Office's Patent Board of Appeals and Interferences. Thirty-five U.S.C. §§ 141, 145. The Federal Circuit was created in 1982 and given the mandate to create uniformity in the patent law. *Panduit Corp. v All States Plastics Mfg. Co.*, 744 F.2d 1564, 1574 (Fed. Cir. 1984). For this reason, and because so few cases are taken by the Supreme Court (which unlike the Federal Circuit has discretion to not hear cases), the decisions of the Federal Circuit are often the final word in patent cases and are of significant precedential value.
5. 383 US 1 (1966).
6. *Graham*, 383 US at 17–18.
7. *Adams*, 383 US at 50–52.
8. *Adams*, 383 US at 50–51.
9. 325 US 327 (1945).
10. 52 US 248 (1851).
11. *Hotchkiss*, 52 US at 266.
12. 92 US 347 (1875).

13. *Reckendorfer*, 92 US at 356–57 (emphasis added). See also *Lincoln Eng'g Co. v Stewart-Warner Corp.,* 303 US 545, 549 (1938) (invalidating a mechanical patent directed to an apparatus for lubricating bearings and stating: 'The mere aggregation of a number of old parts or elements which, in the aggregation, perform or produce no new or different function or operation than that theretofore performed or produced by them, is not patentable invention'.).
14. See, for example, *Eli Lilly & Co. v Generix Drug Sales, Inc.,* 460 F.2d 1096, 1104 (5th Cir. 1972) (chemical compounds present 'riddle wrapped in a mystery inside an enigma' – finding enantiomer is not equivalent of the racemate); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (chemistry is an unpredictable science); *Yamanouchi Pharmaceutical Co. v Danbury Pharmacal, Inc.*, 21 F.Supp.2d 366, 373 n.12 (S.D.N.Y. 1998) (Merck patent on H-2 antagonist famotidine found not obvious: 'Specific note should be taken of the fact that while there are some chemical similarities as to famotidine and a predecessor, tiotidine, the latter had to be abandoned for having unexpected carcinogenic side effects. n12 So much for predictability in the field'.); *In re Tomlinson*, 363 F.2d 928, 932 (C.C.P.A. 1966) (case on chemical stabilisers: 'Considering the evidence as a whole, we think it inescapable that we are here dealing with an art that is quite empirical. Nearly every reference of record speaks of the unexpectedness of the behavior of "related" materials …'); *Studiengesellschaft Kohle mbH v Eastman Kodak Co.*, 616 F.2d 1315, 1341 (5th Cir.) ('[I]n catalytic chemistry, minor changes in components, their ratio, or the external condition of the reaction may produce major changes in the reaction itself'.), *cert. denied*, 449 US 1014 (1980); *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) ('In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved'.).
15. 340 US 147, 166–67 (1950) (emphasis added).
16. See note 4, *supra*, for further discussion of the role of the Federal Circuit.
17. 229 F.3d 1120, 1124–25 (Fed. Cir. 2000) (citing *C.R. Bard, Inc. v M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)).
18. 119 Fed. Appx. 282; 2005 US App. LEXIS 176 (Fed. Cir. Jan. 6, 2005).
19. *Ibid*. 119 Fed. Appx. at 284.
20. *Ibid*. 119 Fed. Appx. at 286.
21. 127 S. Ct. 1727 (2007).
22. *Ibid*. at 1736.
23. *KSR*, 127 S. Ct. at 1741 (emphasis added).
24. *KSR*, 127 S. Ct. at 1742. ('Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle… . A person of ordinary skill is also a person of ordinary creativity, not an automaton'.).
25. *KSR*, 127 S. Ct. at 1742 (emphasis added).
26. See, for example, *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987) ('At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. This is not, however, the standard of 35 U.S.C. § 103'.); *In re Goodwin*, 576 F.2d 375, 377 (C.C.P.A. 1978).
27. 853 F.2d 894, 903 (Fed. Cir. 1988) (emphasis added).
28. 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis added).
29. *KSR*, 127 S. Ct. at 1742 (emphasis added).
30. *KSR*, 127 S. Ct. at 1746 (emphasis added).
31. 314 US 84, 91 (1941).
32. 727 F.2d 1524, 1531 (Fed. Cir. 1984).
33. 480 F.3d 1348 (Fed. Cir. 2007).
34. 325 US 327 (1945) (discussed *supra*).
35. *Pfizer v Apotex*, 488 F.3d 1377, 1383 (Fed. Cir. 2007) (citing to *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963)).
36. See, for example, Glaxo Wellcome, Inc. *v* Pharmadyne Corp., 32 F. Supp.2d 265 (D. Md. 1998).
37. For instance, the authors note that the chemical literature indicated that ether groups (amlodipine contains an ether) may chemically react with benzene sulphonic acids to produce different molecules. See Klamann and Weyerstahl, *Chem. Ber.*, 1965, 98, 2070.
38. 501 F.3d 1254 (Fed. Cir. 2007).
39. Penny LeCouteur, Napoleon's Buttons: How 17 Molecules Changed History, quoted on book jacket (2003).
40. *Daiichi*, 501 F.3d at 1257 ('most of the written description [of the patent] details the inventors' testing ofloxacin on guinea pigs and their finding that ototoxicity did not result').
41. 499 F.3d 1293 (Fed. Cir. 2007).
42. Isomers are molecules that have the same basic atomic constituents, but these atoms are arranged in different ways. An analogy can be made to a person's right hand and left hand – which have the same fingers, but are mirror images to each other that are not super-imposable. Certain types of isomers are called enantiomers – these have a central carbon atom with four different atoms attached to that. A carbon atom with four different attachments is called a 'chiral carbon' and can be

arranged in one of two possible ways. These are often designated, as a matter of nomenclature, as 'S' or 'R'. In addition, enantiomers can be categorised by their ability to rotate polarised light in a clockwise or counterclockwise manner – designated as '+' (also known as dextrorotatory) or '−' (levorotatory). The 'S' and 'R' designation does not necessarily correlate with the physical property of rotation of polarised light ('+' and '−') as 'S' compounds can be '+' or '−' light rotators, as can 'R' compounds. The 'S' and 'R' designations are arbitrary labels related to the weight of atoms attached to the chiral center. Mixtures of both enantiomers of a compound are known as 'racemic mixtures'. Some molecules have multiple 'chiral carbons' where each chiral carbon can exist in one of two configurations – thus there are multiple possible permutations. These multiple possible configurations are called stereoisomers.

43. 499 F.3d at 1300.
44. *Ibid*. at 1301–02.
45. 501 F.3d 1263 (Fed. Cir. 2007).
46. *Ibid*. at 1269.
47. *Ibid*..
48. 491 F.3d 1342 (Fed. Cir. 2007).
49. *Ibid*. at 1362.
50. *Ibid*. at 1363.
51. *Ibid*. at 1367.
52. 483 F.3d 1364 (Fed. Cir. 2007).
53. 492 F.3d 1350 (Fed. Cir. 2007).
54. *Ibid*. at 1356–57.
55. *Ibid*. at 1357.
56. *Ibid*. at 1357–58.
57. *Ibid*. at 1360.
58. 532 F.Supp.2d 666 (D.N.J. 2007).
59. 2007 US Dist. LEXIS 65792 (D.N.J., 6th September, 2007).
60. *Ibid*., 2007 US Dist. LEXIS 65792 at *5.
61. *Ibid*., 2007 US Dist. LEXIS 65792 at *16 to *22.
62. 516 F.Supp.2d 238 (S.D.N.Y. 2007).
63. 482 F.Supp.2d 478 (D.N.J. 2007).
64. 2008 US App. LEXIS 15399 (Fed. Cir., 21st July, 2008).
65. *Esai*, 2008 US App. LEXIS 15399 at *5–6 and *11–12.
66. 520 F.3d 1358 (Fed. Cir. 2008).
67. *Ibid*. at 1364–65.
68. *Ibid*.
69. Smith, A. (1776). Wealth of Nations', Book V, Chapter 1.
70. Arias, E. (2004). United States life tables, 2000', National Vital Statistics Reports 52, No. 14, Table 11.
71. *MedImmune, Inc. v Genentech, Inc.*, 127 S. Ct. 764 (2007) (easing the standard for allowing declaratory judgment actions against patents to be brought in federal court).
72. See, for example, *Festo v Shoketsu Kinzoku*, 493 F.3d 1368 (Fed. Cir. 2007) (weakening infringement under the doctrine of equivalents by holding that estoppel bars equivalents for 'foreseeable' alternatives – even where the particular alternative was not specifically known to be interchangeable in the context of the invention at issue).
73. *Ebay Inc. v MercExchange LLC,* 547 US 388 (2006) (clarifying requirements for issuance of an injunction in a patent case).
74. *In re Seagate*, 497 F.3d 1360 (Fed. Cir. 2007) (holding that to prove willful infringement requires more than a showing under a negligence-type standard, but a showing of 'objective recklessness').
75. Churchill, W., 6th September, 1943 speech at the Harvard University.