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From Allergan to BMS: Are We Forgetting the Lessons of History?

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The authors review recent Federal Circuit decisions on obviousness of pharmaceutical compositions and argue that counsel and courts are making missteps contrary to lessons learned in the three decades after the 1952 Patent Act established Section 103.

I. Introduction

It is often said that those who would ignore history are doomed to repeat it. It is important, therefore, in moving forward in the law to revisit from time to time the historical development of seemingly familiar legal principles to avoid repeating missteps that were made and corrected by those who walked this road before us. Nowhere is this more important than in the determination of obviousness under the patent law in the economically and socially important field of the pharmaceutical sciences. Here, federal courts should be particularly careful in assessing obviousness for a variety of reasons.

First, by definition, we are dealing with novel compositions and methods in assessing obviousness. By the time the issue reaches the federal district court, the U.S. Patent and Trademark Office (PTO) will already have determined that the invention was nonobvious, the Food and Drug Administration (FDA) will already have determined that the invention is safe and effective in treating disease, a decade of effort and hundreds of millions of dollars will already have been expended in discovering and testing the invention, and the product will have been sufficiently successful in the marketplace to have provoked efforts to copy it. Making the wrong judicial call under these circumstances has dire consequences not only in the particular case but, in the aggregate, on the incentive to make the massive, long-term investments required for research and development in this field. Stability in the law in this area is of paramount importance.

A review of recent Federal Circuit decisions suggests that we may be losing sight of early lessons solidified by the enactment of 35 U.S.C. § 103 in 1952 and the efforts of the Court of Customs and Patent Appeals (CCPA) in the ensuing three decades to develop a coherent and usable body of obviousness jurisprudence in the pharmaceutical arena. There is an inevitable temptation to ignore the "old" as somehow less relevant to the "present," but the Greeks got a lot right about mathematics and political science, and the courts struggled for 150 years with what made an invention patentable before adopting the statutory test embodied in Section 103, and lots of smart, thoughtful people have given much thought to how to apply that standard in the pharmaceutical arena in the ensuing 60 years. This brief review is offered in the hope that a reminder not to forget the past will help new generations of advocates and judicial decision makers avoid repeating historical mistakes.

II. Remember the Statute

The lessons learned from 150 years of attempting to describe that which makes a novel development a patentable invention were embodied in pre-AIA 35 U.S.C. § 103 enacted in 1952.[1] It reads, in pertinent part:

> 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 negative by the manner in which the invention was made.

The statute is carefully worded and provides an objective, evidence-based standard for assessment of obviousness. When properly applied, the statute protects judicial decision makers from the insidious effect of hindsight, which is the greatest single obstacle in accurately assessing obviousness. The following essential lessons emanate from the statutory language:

- The statute's requirement that the invention and prior art be considered from the *perspective of a hypothetical person having ordinary skill in the art* to which the subject matter pertains is an *objective* standard focused on the perceptions of ordinary scientists, not laymen, not lawyers, and not even judges. It is a judgment that must be made based on *evidence* of the perceptions and skills of such a scientist.

- Section 103 mandates that obviousness be determined *at the time the invention was made*, requiring decision makers to cast their minds back to a time before the invention was known. This is incredibly difficult for most people to do because most inventions, once understood, seem obvious. The statute reinforces the need to rely on the evidence of earlier beliefs rather than on such subjective reactions.

- It is the obviousness of the claimed *subject matter as a whole* that is to be determined, not just pieces of it and not just the points of difference from the prior art. This point is particularly important in the pharmaceutical area where, as we shall see, it is not just the structure of new compositions that must be considered but their constellation of properties as well.

- The statute requires consideration of "the" prior art, not just part of it. It is as important to consider the prior art as a whole, including prior art suggesting a path different from that followed by the inventor, as it is to consider the invention as a whole.

- The statute specifically states that patentability shall not be negatived by the manner in which the invention was made. In other words, an inventor's own work, insights, expectations and approaches are not evidence of obviousness. Obviousness is determined from the perspective of a person having ordinary skill in the art, not that of an inventor.[2]

- The statute imposes no requirement of "importance," "superiority" or "commercial value" as a condition of patentability.[3] Perfectly nonobvious and patentable inventions can be made throughout the spectrum of activities involved in pharmaceutical product development. While the Nobel Prize might be awarded for the discovery of a cancer cure, "Patents are not Nobel or Pulitzer prizes."[4] Thus, patents can and should be sustained on unobvious new uses, new salt forms, new crystal

[1] AIA Section 3(c), 125 Stat. 287, amends 35 U.S.C. § 103 and shifts the relevant time somewhat (from "as of the date of the invention" to "before the effective filing date of the claimed invention"), but still requires casting the mind back to an earlier time and still requires that ALL the art available at that time be considered.
[2] *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293 (Fed. Cir. 1985).
[3] Rich, Giles S., Principles of Patentability, 28 Geo. Wash. Law Rev., No. 2, 393 (1960).
[4] *Id.* at 401.

forms, new manufacturing methods and new formulations. Many such patents are easily avoided, but some are not. The applicable standard of patentability, however, remains the same in all cases.

Some 60 years of experience operating under the statute have yielded a number of insights. Two are particularly worth mentioning. The first is the importance of evidence of *unpredictability* in assessing obviousness. This concept is intrinsically tied to the "art to which said invention pertains" referred to in the statute. Some technologies are highly predictable. In certain mechanical arts, for example, the person of ordinary skill can envision from the disclosure of a single embodiment a wide variety of operable variations. But some technologies are highly unpredictable, whereby a discovery related to one embodiment simply does not permit rational extrapolation to other embodiments due to the unpredictable nature of the field. Even the Supreme Court, in its most expansive statements regarding determinations of obviousness, has noted that obvious solutions must have been *predictable*.[5] There are few fields less predictable than the pharmaceutical arts, where unpredictability of properties arising from changes in composition is multiplied by unpredictability of effects and side effects of compositions in living subjects.

Second, there is no shortcut to the objective, evidence-based, hindsight-free analysis required by the statute. In years gone by, one could often see in the reported cases what came to be known as "negative rules of invention." These were bright line rules, such as "a mere change of form is not invention;" "a mere change of degree is not invention;" "a mere substitution of material is not invention;" "substitution of equivalents in an old combination is not invention;" and "a mere aggregation of elements is not invention."[6] While such negative rules found favor with some because a bright line test is easy to apply, these "rules" state ultimate conclusions rather than provide guidance for analyzing the evidence. The statute makes clear that there is one analysis and one standard in the law of obviousness. There are no shortcuts.

III. Remember the CCPA

Following enactment of 35 U.S.C. § 103, there was no court that dealt more frequently with its application to pharmaceutical technologies than the CCPA, which reviewed all the patentability determinations arising out of the PTO.[7] CCPA decisions in the field of pharmaceutical obviousness are particularly instructive for a variety of reasons. First, that court always sat en banc, with five judges hearing argument in every case. Second, that court made and ultimately corrected many mistakes in applying the law of pharmaceutical obviousness, and awareness of that process will help to avoid repeating those same mistakes. Finally, those decisions are with us still, because the Federal Circuit has adopted the decisions of the CCPA as binding precedent.[8] We note here a few of those decisions that seem to be of current interest.

A. How Do We Evaluate Obviousness?

After many, many missteps in the analytical approach to assessing obviousness, where some evidence was considered only when the issue was in doubt, it is now well settled that *all* of the evidence bearing on the issue of obviousness must be considered.[9] In the early days of assessing obviousness in cases arising from the PTO, where there was no statutory presumption of validity, the CCPA adopted a burden shifting approach.[10] Once the PTO made out a "prima facie case" of obviousness the burden shifted to the applicant to come forward with evidence that the invention was nonobvious.[11] This approach led to unfortunate situations in which the initial conclusion that *some* of the evidence established a prima facie case took on a life of its own, with any new evidence being considered only for its ability to "knock down" the preliminary conclusion.

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[5] *KSR Int'l Co., v. Teleflex Inc.*, 550 U.S. 398, 416, 2007 BL 12375, 82 U.S.P.Q.2d 1385 (2007) (74 PTCJ 5, 5/4/07).
[6] Eugene D. Sewell, Law of Patents 36 (American School of Correspondence 1912).
[7] "PTO" is used broadly to also include the pre-1975 Patent Office.
[8] *South Corp. v. U.S.*, 690 F.2d 1368, 1369, 215 U.S.P.Q. 657 (Fed. Cir. 1982).
[9] *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539, 218 U.S.P.Q. 871 (Fed. Cir. 1983).
[10] *See In re Rinehart*, 531 F.2d 1048, 1052, 189 U.S.P.Q. 143 (C.C.P.A. 1976).
[11] *Id.*

By 1976, however, the CCPA realized that this approach distorted the analysis required by the statute, which required consideration of all of the relevant evidence.[12] *In re Rinehart* held that the final step of an obviousness analysis required the entire path to an obviousness decision to be retraced in light of *all* of the available evidence.[13] It was improper, the court held, to evaluate evidence of nonobviousness only for its "knockdown ability" against a preliminary obviousness determination.[14]

B. How Do We Evaluate Unexpected Results?

A very common type of evidence arising in the generally unpredictable pharmaceutical field is evidence of one or more unexpected properties manifested by the claimed invention. The CCPA had considerable difficulty sorting out how to handle such evidence. Early on, it was suggested that the obviousness of compositions should turn solely on analysis of their structure, and that newly discovered properties should result only in method-of-use patents.[15] That view started to change in 1963.

1. *In re Papesch*

In *In re Papesch*, the claimed compound, which the examiner rejected and the Patent Office Board of Appeals affirmed as obvious, differed from a structurally similar prior art compound by only three -CH_2 groups and was presumed to share many common properties.[16] The PTO maintained the rejection despite the applicant establishing that the claimed compound possessed unexpectedly potent anti-inflammatory activity where the prior art was completely inactive in that respect.[17] The CCPA reversed, finding the single unexpected property sufficient to establish nonobviousness.[18]

The PTO predicated its rejection on the mistaken theory that "[a]n unexpected difference in a single property should not be adequate to support a claim for a novel, but obvious, homologue . . . ."[19] In response, Judge Giles S. Rich, writing for the CCPA, reviewed a long line of cases dealing with obviousness, both before and after the enactment of Section 103 in 1952, in which new chemical compounds were found nonobvious in spite of close structural similarity to the prior art after taking into consideration their unexpected biological or pharmacological properties.[20] The indisputably correct reason for so holding is that the presumptive similarity in properties arising from "obvious" structural similarity must yield to the evidence that the similarity in predicted properties is not, in fact, true.[21]

In reversing the obviousness rejection, the CCPA reasoned that the Board's failure to consider the unexpected properties of the Papesch compound was a fundamental error that ran contrary to well established law.[22] Most notably, the court held that "a compound and all of its properties are inseparable; they are one and the same thing."[23]

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[12] *Id.*
[13] *Rinehart*, 531 F.2d at 1052.
[14] *Id.*
[15] *See In re Papesch*, 315 F.2d 381, 391, 137 U.S.P.Q. 43 (C.C.P.A. 1963).
[16] *Id.* at 383, 391.
[17] *Id.* at 383–84.
[18] *Id.* at 392.
[19] *Id.* at 384.
[20] *Id.* at 387-391 (discussing *In re Petering*, 301 F.2d 676, 133 U.S.P.Q. 275 (C.C.P.A. 1962), *In re Lambooy*, 300 F.2d 950, 133 U.S.P.Q. 270 (C.C.P.A. 1962), *In re Larsen*, 292 F.2d 531, 130 U.S.P.Q. 209 (C.C.P.A. 1961), *In re Bergel*, 292 F.2d 955, 130 U.S.P.Q. 206 (C.C.P.A. 1961), *Sterling Drug, Inc. v. Watson*, 135 F. Supp. 173 (D.D.C. 1955), *Ruskin v. Watson*, 123 F. Supp. 33 (D.D.C. 1954), *In re Schechter*, 205 F.2d 185, 98 U.S.P.Q. 144 (C.C.P.A. 1953), *Parker v. Marzall*, 92 F. Supp. 736 (D.D.C. 1950), *Schering Corp. v. Gilbert*, 153 F.2d 428, 68 U.S.P.Q. 84 (2d Cir. 1946), *In re Hass*, 141 F.2d 122, 60 U.S.P.Q. 544 (C.C.P.A. 1944).
[21] *Id.* at 391.
[22] *Id.* at 391–92.
[23] *Id.* at 391.

2. *In re Lunsford*

There were also some missteps in dealing with cases where the prior art and the claimed invention both had the same property but to different degrees. A few years after *Papesch*, the CCPA decided *In re Lunsford*.[24] Mr. Lunsford admitted that the claimed compound was structurally similar to the prior art compound, and that both the claimed compound and the prior art compound were anti-convulsants.[25]

However, Mr. Lunsford established that his compound exhibited a "significant, advantageous, unexpected difference" in properties—it was unexpectedly superior in anti-convulsant activity, being some 4.4 to 7 times as potent as the prior art compound.[26] Reversing the Board's affirmance of obviousness, the CCPA found that a difference existed rendering the invention patentable because Mr. Lunsford's compounds "possess anticonvulsant activity substantially greater than the prior art compound," which was "unpredictable from the prior art."[27]

3. *In re May*

By 1978, it was clear that unexpected properties relating not only to efficacy but also to side effects were pertinent to the pharmaceutical obviousness analysis. *In re May*[28] involved a claimed compound that was both analgesic and nonaddictive. Analgesics were a dime a dozen. Nonaddictive analgesics were not.[29] The Board rejected the claims, noting that it would have been obvious to make the new compound for its expected analgesic effect.[30] As in *Lunsford*, Appellants framed the issue on appeal as whether the compound's unexpectedly superior property of nonaddictiveness established nonobviousness.[31]

The *May* court noted that the basis for the PTO's obviousness determination, at least to a major extent, was the presumed expectation that compounds with similar structures will have similar properties.[32] The CCPA, however, stated that an actual difference in properties is not the only way to establish nonobviousness.[33] Sufficient evidence demonstrating a substantial degree of unpredictability may also suffice.[34] Balancing the compound's expected analgesia property versus its unexpected nonaddictiveness, and noting that Appellants had "established a substantial record of unpredictability," the May court concluded that the claimed invention was nonobvious.[35]

4. *In re Ruschig*

The issue of the effect on the obviousness analysis of toxicity of the prior art compounds was addressed early on by the CCPA in *In re Ruschig*.[36] The CCPA there reversed the Board's affirmance of obviousness rejections of several genus and species compound claims.[37] The *Ruschig* court discussed that when a prior art compound has similar therapeutic properties but is so toxic that it is wholly unusable as a drug, the "[v]ery high toxicity . . . cancels out any notion of [therapeutic] 'utility'."[38] That the state of the pharmaceutical arts is such that toxicities cannot be predictably eliminated is clear from (1) the fact that the FDA requires that toxicity be

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[24] *In re Lunsford*, 357 F.2d 380, 148 U.S.P.Q. 716 (C.C.P.A. 1966).
[25] *Id.* at 381.
[26] *Id.* at 381, 385.
[27] *Id.* at 385.
[28] *In re May*, 574 F.2d 1082, 1088-89, 197 U.S.P.Q. 601 (C.C.P.A. 1978).
[29] *See id.*
[30] *Id.* at 1089.
[31] *Id.* at 1089-91.
[32] *Id.* at 1094.
[33] *Id.*
[34] *Id.*
[35] *Id.* at 1093–95.
[36] *In re Ruschig*, 343 F.2d 965, 145 U.S.P.Q. 274 (C.C.P.A. 1965).
[37] *Id.* at 966, 979.
[38] *Id.* at 976, 978.

independently evaluated for each new compound, and (2) the number of clinical trial candidates that fail for unanticipated toxicity even in late stage testing.

5. *In re Chupp*

The early Federal Circuit decisions remained true to earlier developments in the CCPA. In *In re Chupp*,[39] for example, a single compound was claimed, which differed from the closest prior art compound by a single methylene group.[40] Mr. Chupp responded to the PTO obviousness rejection by providing affidavits to show, with respect to two crops, corn and soybean, the claimed compound had "unexpected and unpredictable superiority in terms of its combination of crop safety and weed killing activity in comparison to the prior art."[41] But the Chupp compound was *not* superior to the prior art on every crop.[42]

The court considered the unexpected properties and, applying the principles of the CCPA's *Papesch* decision, the Federal Circuit held that nonobviousness evidence "may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds."[43] Reversing the Board, the Federal Circuit reasoned that "[e]vidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness."[44]

In the aggregate, the CCPA jurisprudence confirmed that all the properties of a new pharmaceutical composition were to be considered in assessing obviousness, including differences in efficacy, side effects and toxicity in relation to the prior art. That court equally held that the essence of the analysis focused on the significance of the newly discovered property and the predictability of the newly discovered effect, and the Federal Circuit has confirmed that an unexpected difference in one of a spectrum of shared properties could suffice. Basing pharmaceutical nonobviousness on unpredictability and unexpected results, as in these cases, is entirely consistent with the more recent pronouncements of the Supreme Court in *KSR*, which predicated an obviousness finding on the availability of a finite number of *predictable* solutions to a problem.[45] These are sound rules that took a long time to develop, and we should avoid re-making the mistakes of our predecessors.

IV. Are We Re-Making Old Mistakes?

Some recent decisions raise the issue of whether judicial decision makers are being led into re-making old mistakes by a new generation of advocates who have themselves forgotten or never knew the old lessons. A few examples illustrate the point.

A. *Allergan v. Sandoz*

In its *Allergan v. Sandoz*[46] decision, the Federal Circuit agreed with the district court that the efficacy and safety of Allergan's Combigan product was unexpected and that such evidence was relevant to uphold the validity of a patent claiming the method of administering the product twice a day.[47] Specifically, a twice per day regimen of Combigan (0.2% brimonidine and 0.5% timolol) unexpectedly did not result in the typical "afternoon trough" associated with the same dosing regimen of 0.2% brimonidine alone.[48]

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[39] *In re Chupp*, 816 F.2d 643, 2 U.S.P.Q.2d 1437 (Fed. Cir. 1987).
[40] *Id*. at 644.
[41] *Id*. at 644-45.
[42] *Id*. at 645.
[43] *Id*. at 646 (citing *Papesch* and *Lunsford*).
[44] *Id*. at 646.
[45] *KSR*, 550 U.S. at 421-22.
[46] *Allergan, Inc. v. Sandoz Inc*., 726 F.3d 1286, 2013 BL 115500, 106 U.S.P.Q.2d 1574 (Fed. Cir. 2013) (86 PTCJ 15, 5/3/13).
[47] *Id*. at 1293-94.
[48] *Id.* at 1289, 1293.

The court, however, found that those same unexpected results were *not* similarly meaningful to a second patent with composition claims covering the underlying combination product and were insufficient to outweigh the other evidence of obviousness against those claims.[49]

Has the rationale of *Papesch*, that unexpected properties of a composition are relevant to the nonobviousness of the composition been lost here? Judge Dyk, dissenting in part from the affirmance of the validity of the method claim, argued that the different results between the method and composition claims cannot be reconciled.[50]

B. *Novo Nordisk v. Caraco*

In *Novo Nordisk v. Caraco*,[51] the PTO allowed Novo's method claim for treating Type II diabetes involving administration of a combination of two drugs, repaglinide and metformin, based on Novo's discovery that the combination had an unexpected synergistic therapeutic effect.[52] That is to say, the effect of the combination unexpectedly exceeded the hypothetical additive effect of administering repaglinide and metformin separately.[53]

When repaglinide and metformin were administered to a subpopulation of Type II diabetes patients failing on metformin treatment, the combination resulted in blood glucose levels more than *eight* times lower than levels achieved after administering metformin alone.[54] Novo conducted further testing in an animal model of diabetes, the results of which only further supported its conclusion that the combination surprisingly exhibited synergistic effects in reducing blood glucose levels.[55] Despite the combination's synergistic properties, the Federal Circuit affirmed the district court's ruling that Novo's combination therapy claim was obvious.[56]

Novo asserted that the combination's synergistic effect was surprising considering repaglinide administered alone was known to have no impact on blood glucose levels.[57] In the court's view, however, the closest prior art was not repaglinide monotherapy, but a combination therapy using metformin and a sulfonylurea (a class of insulin secretagogues that does not include repaglinide).[58] In particular, the combination of metformin and glyburide was known in the art to produce synergistic effects in controlling glucose levels in Type II diabetes patients, whereby the synergistic effect of Novo's composition was alleged to have been expected.[59] The Federal Circuit found no clear error in the finding that the claimed combination's synergistic effect was expected when compared to the closest prior art.[60]

But glyburide is structurally different from repaglinide.[61] Repaglinide was known as a short-acting and glyburide was known as a long-acting insulin secretagogue.[62] And when administered as a monotherapy, repaglinide was known to have no impact on blood glucose levels whereas glyburide alone was known to

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[49] *Id.* at 1293.
[50] *Id.* at 1295.
[51] *Novo Nordisk A/S v. Caraco Pharm. Labs, Ltd.*, 719 F.3d 1346, 2013 BL 159787, 106 U.S.P.Q.2d 1574 (Fed. Cir. 2013) (86 PTCJ 398, 6/21/13).
[52] *Id.* at 1349-51.
[53] *Id.* at 1349.
[54] *Id.* at 1349.
[55] *Id.* at 1350.
[56] *Id.* at 1348.
[57] *Id.* at 1355.
[58] *Id.* at 1349, 1355.
[59] *Id.* at 1355, 1363.
[60] *Id.* at 1355.
[61] *Id.* at 1364.
[62] *Id.*

reduce blood glucose levels.[63] And even combining metformin and a sulfonylurea was shown to have unpredictable effects on glucose levels as only some combinations showed a synergistic effect.[64]
Has the need for reasonable predictability in pharmaceutical obviousness been overlooked here? As Judge Newman explained in her dissent, "[t]he existence of synergy in some metformin-sulfonylurea combinations is not predictive of synergy in the combination of metformin with repaglinide."[65] It would appear that fair ground for further research was presented here, but not a finite number of predictable solutions of the sort envisioned by KSR.

C. *Galderma v. Tolmar*

In *Galderma v. Tolmar*,[66] a divided Federal Circuit panel reversed the district court's ruling that claims directed to Differin Gel, 0.3%, Galderma's topical anti-acne medication containing 0.3% adapalene were nonobvious.[67]

Prior patents disclosed topical adapalene formulations for the treatment of acne in concentration ranges encompassing 0.3%, but not the specific use of 0.3% adapalene.[68] At the time of the invention, 0.1% was reported to be the optimal concentration of adapalene for the treatment of acne based on both efficacy and safety, and was commercially available for that use.[69] An increase in dose from 0.1% to 0.3% (a 300% increase) was expected to result in a clinically significant increase in side effects.[70] Unexpectedly, however, the inventors' tests in actual patients showed that tolerability profiles associated with 0.1% and 0.3% adapalene were comparable.[71]

The majority held that the challenger satisfied its burden for establishing obviousness simply by pointing to "where there is a range disclosed in the prior art, and the claimed invention falls within that range," without further reason to select the claimed invention and without consideration of later evidence negating any motivation to select the claimed invention.[72] Specifically, a very early generic disclosure relating to the use of a family of compounds encompassing adapalene, published long before the prior art discovered the optimal safety of the 0.1% product, nonetheless disclosed a 100-fold dose range that encompassed the later-claimed 0.3% dose.[73]

In her dissenting opinion, Judge Newman explained how the majority's "new law" runs afoul of a challenger's burden to overcome the statutory presumption of validity with clear and convincing evidence of obviousness.[74] According to Judge Newman, the majority's "dismissive analysis" unduly presumes that a broad teaching without more removes the statutory presumption of validity, establishes obviousness, and places on the patentee the burden of establishing patentability based on secondary considerations.[75]

In failing to consider evidence negating any motivation to select the claimed invention at the time that invention was actually made, has the requirement established by statute and reinforced by precedent that

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[63] *Id.* at 1364.
[64] *Id.* at 1360.
[65] *Id.* at 1361.
[66] *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 2013 BL 342800, 106 U.S.P.Q.2d 1574 (Fed. Cir. 2013) (87 PTCJ 324, 12/13/13). Finnegan, Henderson, Farabow, Garrett, and Dunner LLP represented Galderma in this case. Ms. Henninger appeared on behalf of Galderma in the district court case, *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 891 F. Supp.2d 588, 2012 BL 344052 (D. Del. 2012).
[67] *Galderma*, 737 F.3d at 734.
[68] *Id.* at 736, 743.
[69] *Id.* at 735, 738, 744.
[70] *Id.* at 738.
[71] *Id.* at 739, 748.
[72] *Id.* at 737-38, 749.
[73] *Id.* at 743-45.
[74] *Id.* at 741-42.
[75] *Id.*

obviousness be determined by assessing all the evidence as a whole been overlooked? Need we heed the CCPA's reminder in *Rinehart* that the last step in the analysis involves reconsideration of *all* of the evidence as a whole before reaching any conclusion regarding obviousness?

D. *BMS v. Teva*

More recently, in *Bristol–Myers Squibb v. Teva*,[76] the Federal Circuit agreed with the district court's finding that entecavir, the active ingredient of BMS's hepatitis B drug, Baraclude, exhibits unexpectedly superior therapeutic properties.[77] Yet, both *BMS* courts found that entecavir would nonetheless have been obvious.[78] Have old lessons been overlooked here as well?

In particular, the district court determined that the biological properties of entecavir, "such as its high potency, high barrier to resistance and the size of its therapeutic window," were "beyond what was expected at the time of the invention."[79] Indeed, the district court found entecavir to be "more potent *in vitro* than every other compound."[80] Even the Federal Circuit agreed that entecavir's high level of effectiveness and high genetic barrier to resistance were unexpected properties.[81] Such unexpectedly superior efficacy would have sufficed historically under cases like *Lunsford* to establish nonobviousness.

The *BMS* court relied upon yet another of its recent decisions on pharmaceutical obviousness, *Roche v. Apotex*.[82] In *Roche*, the Federal Circuit found Roche's Boniva product, a monthly oral dosing regimen of 150 mg of ibandronate to treat osteoporosis, resulted in unexpected efficacy, but nevertheless found the dosing regimen obvious.[83] The *Roche* court stated, "The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected."[84] Both here and in *Galderma*, it appears that a determination might have been made that a result that was unexpected by scientists was simply not big enough in the eyes of judges to satisfy the statutory nonobviousness test. But should not the evidence based test of whether the effect was unexpected to persons skilled in the art answer the question of degree as well? As it was with the old negative rules of invention, saying a result is a mere difference in degree and not a difference in kind is to state a conclusion unmoored from the statutory analysis it has replaced.

The issue of unexpected avoidance of side effects was also implicated in *BMS*. Both courts found entecavir's anti-hepatitis activity and safety to be expected because, at the time of entecavir's invention, 2'-CDG (characterized by the *BMS* courts as a "lead compound") was known to have activity against hepatitis B and was thought to be safe.[85] But unlike FDA-approved entecavir, 2'-CDG and Madhavan 30 (another prior art compound relied on by the *BMS* courts) are toxic.[86] Indeed, the district court found that the "most significant difference between 2'-CDG and entecavir is that the former is toxic while the latter is not."[87] And "[o]f the analogs made by the Madhavan group, they found that Madhavan 30 was the most potent, but also the most toxic."[88] Have the lessons of *Ruschig* been lost here? Should any therapeutic properties associated with 2'-

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[76] *Bristol–Myers Squibb Co. v. Teva Pharms USA, Inc.*, No. 13-1306, 2014 BL 163648, 111 U.S.P.Q.2d 1293 (Fed. Cir. June 12, 2014) (88 PTCJ 527, 6/20/14).
[77] *Id.* at *9.
[78] *Id.* at *1.
[79] *Bristol–Myers Squibb Co. v. Teva Pharms USA, Inc.*, 923 F. Supp.2d 602, 685-86, 2013 BL 36108 (D. Del. 2013).
[80] *Id.* at 685.
[81] 2014 BL 163648 at *9.
[82] Id. at *8-9 (quoting *Hoffmann-La Roche Inc. v. Apotex Inc.*, 2014 BL 101477, at *7, 110 U.S.P.Q.2d 1494 (Fed. Cir. April 11, 2014) (87 PTCJ 1427, 4/18/14)).
[83] *Id.*
[84] *Id.*
[85] *Id.* at *2, *4-5, *9.
[86] *Id.* at *5, *6; 923 F. Supp.2d at 626, 628.
[87] 923 F. Supp.2d at 626.
[88] *Id.* at 628.

CDG and Madhavan 30, including anti-hepatitis activity, have been cancelled out on account that both compounds are toxic, as they were in *Ruschig*?

V. Where Do We Go From Here?

We raise here the possibility that a new generation of decision makers in cases like *Allergan*, *Novo Nordisk*, *Galderma* and *BMS* may be falling prey to some of the same missteps that beset earlier generations of decision makers in this complex and important area of the law. The overarching point is that practitioners and judicial decision makers both need to heed the lessons of history in applying the statutory obviousness standard in the pharmaceutical field if we are to avoid repeated cycles of making and correcting the same mistakes. Because the development investments in this field are long-term, not uncommonly consuming a decade or more, stability in this area of the law is particularly important.

Cases raising these issues arose with some regularity before the Federal Circuit. The court only recently decided the *BMS* case, and others are on the way. There is no need to reinvent the wheel in terms of avoiding hindsight; making objective decisions based on all of the available evidence; recognizing that the entire spectrum of therapeutic properties, side effects and toxicities of pharmaceutical compositions are relevant to the obviousness inquiry; and appreciating the importance of reasonable predictability to any proper obviousness finding in the pharmaceutical field.

As the wise have often said "When you think you have thought of something truly original, look back and see how the Greeks said it."