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Secondary Considerations in Pharmaceutical Patents: Part One

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Introduction and Background

Obviousness rejections under 35 U.S.C. § 103 are probably the most subjective of all rejections received during the prosecution of a patent, and they are also one of the most common. Every patent practitioner can most likely recite the *Graham* factors used for an obviousness analysis: 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) analyzing any secondary considerations of non-obviousness. *Graham v. John Deere*, 383 U.S. 1 (1966). Of the four *Graham* factors, it is the issue of secondary considerations that creates difficulty for Examiners, patent attorneys and judges alike. Sometimes referred to as ''objective indicia,'' many patent attorneys wonder how significant a role they play in an obviousness analysis or if they are only used to confirm what an Examiner or a Court has already decided. In the pharmaceutical industry, this question is especially relevant.

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Secondary considerations are intended to play a role equal to or greater than the other *Graham* factors in an obviousness analysis. The Federal Circuit has stressed the importance of evaluating all four factors before making an obviousness determination:

''It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called 'secondary considerations' must ***always*** when present be considered en route to a determination of obviousness. . .Indeed, evidence of secondary considerations may often be the ***most probative and cogent evidence in the record***. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, ***not just when the decisionmaker remains in doubt after reviewing the art*** (emphasis added).'' *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1076 (Fed. Cir. 2012) citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

Obviousness and patent validity are often litigated in the pharmaceutical industry until all possible appeals have been exhausted because a single patent may be all that protects a marketed pharmaceutical product from generic competition. When a putative generic manufacture wants to enter the market before the expiration of all of the patents covering a marketed product, litigation under the Hatch-Waxman Act ensues. 21 U.S.C. § 355 *et seq*. An Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration is one of the early steps taken by a putative generic manufacturer and often leads to litigation. Secondary considerations are often argued during ANDA litigation when

a generic manufacturer asserts that a patent is invalid for being obvious. These cases often result in Federal Circuit decisions that illustrate the evidence required to successfully refute an assertion of invalidity under 35 U.S.C. § 103. Secondary considerations may also be argued to the Patent Office during prosecution of the application. Because of the frequency in which secondary considerations may be used during both patent prosecution and infringement litigation in connection with obviousness, understanding the evidentiary requirements for such an analysis is critical.

This is the first in a pair of articles that break secondary considerations into two groups: pre-patenting (Part One) and post-patenting (Part Two). Pre-patenting secondary considerations are those that usually occur before a patent issues and may be available to introduce during prosecution of the application. They include long felt need, failure of others, unexpected results, and skepticism of experts. Post-patenting secondary considerations typically arise after a patent has been issued and are most often argued during litigation. They include commercial success, praise by others, copying by others, and simultaneous invention. They are often not available during prosecution of the application.

Pre-Patenting Secondary Considerations Pre-patenting secondary considerations include long-felt need, failure of others, unexpected results and skepticism of experts. In many cases, they are available to argue during prosecution of the application. Sometimes the material is included directly in the application during drafting (e.g., unexpected results included in the Examples, or a discussion of an unmet need in the Background section) and can be argued if (when) an obviousness rejection occurs. In other instances, evidence of any secondary considerations may be introduced via an inventor's declaration under 37 C.F.R. § 1.132 in response to an obviousness rejection. Either way, understanding what evidence is and isn't persuasive is critical in overcoming an Examiner's rejection. During litigation, expert testimony regarding any secondary considerations will usually be critical in persuading a court to uphold the validity of a patent against an assertion of invalidity under 35 U.S.C. § 103.

■ Long-Felt Need

Long-felt need, also referred to as an unmet need or unsolved need in court decisions, requires a person having skill in the art to recognize that the need existed at the time of invention, not afterward. *In re Gershon*, 372 F.2d 535, 538, (CCPA 1967). Being the first person to recognize and solve a problem may be an excellent argument in support of novelty; however, this evidence may lead to a different conclusion in regard to secondary considerations:

''[s]ince the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long-felt need. . . for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware (citation omitted).''*Id*.

Olanzapine, sold under the trade name of Zyprexa® and originally marketed by Eli Lilly as an atypical antipsychotic for the treatment of schizophrenia and bipolar disorder, is structurally similar to clozapine which was used as the lead compound in the obviousness rejections during prosecution of US Patent No. 5,229,382. It was also a significant factor in the arguments presented during ANDA litigation. Eli Lilly presented a strong showing of secondary considerations, including information illustrating the long felt need to develop a safer and more effective antipsychotic medication. *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 364 F. Supp.2d 820 (S.D. Ind. 2005) affirmed in *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 471 F.3d 1369 (Fed. Cir. 2006). Testimony accepted as part of the Findings of Fact and Conclusions of Law at trial established that beginning at least 15 years prior to the discovery of olanzapine, ''[t]he medical need for better antipsychotic drugs in terms of increased efficacy and fewer unwanted effects is great'' and that a significant number of investigators were simultaneously working to develop a similarly safe and effective antipsychotic drug. *Eli Lilly*, 364 F. Supp.2d at 852, facts 185 and 186. There was also a clear need ''reflected in the scientific literature'' to find a replacement for clozapine, the best available treatment at the time, due to the significant side effects experienced by patients, including movement disorders, bone marrow suppression and seizures. *Id*. at 832, fact 21.

The approach utilized by Eli Lilly, *supra*, and affirmed by the Federal Circuit, has been used in other courts during ANDA litigation where obviousness is argued by a generic manufacturer attempting to invalidate any patents being asserted to prevent the generic launch. Risedronate is sold under the tradenames of Actonel®, Atelvia® and Benet® and was originally developed by Warner Chilcott for the treatment of osteoporosis. During risedronate ANDA litigation, Warner Chilcott introduced uncontested evidence that beginning in the mid-1980s (over 10 years prior to the filing of the patent) that osteoporosis was recognized as a serious disease and that then-existing treatments were inadequate. *Procter & Gamble v. Teva Pharmaceuticals*, 536 F. Supp.2d 476 (D. Del. 2008) affirmed in *Procter & Gamble v. Teva Pharmaceuticals*, 566 F.3d 989 (Fed. Cir. 2009) (Note that there is a typographical error in the opinion. The '122 patent is US 5,583,122, not US 5,588,122). Teva argued that a competing drug was already on the market when risedronate was approved for use, so there was no unmet need. The court rejected the argument that the unmet need must be present at the time the invention receives approval for commercial marketing by the U.S. Food and Drug Administration (FDA), rather than during development, and determined that the filing date of the application is when the long-felt and unmet need determination is made. *Procter & Gamble*, 566 F.3d. at 998 citing *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877 (Fed. Cir. 1998). An unaddressed question is what would happen if development of a drug began when there was a long-felt or unmet need but a competing product came to market *before* the patent application is filed?

Dronedarone, marketed under the tradename of Multaq® by Sanofi-Aventis as an antiarrhythmic drug (AAD), similarly presented strong supporting evidence in the prior art that supported a finding of long-felt and unmet need. It was known and well documented that there was an unmet need for an antiarrhythmic drug (AAD) that exhibited both rate and rhythm control for the heart rate of a patient while exhibiting a favorable

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side effect profile. Despite the fact that there were multiple AADs on the market when the patent application for dronedarone was filed, expert testimony established that ''it has been notoriously difficult to develop [an AAD] with a high efficacy against [atrial fibrillation] with a favorable side effect profile'' and that there was ''an urgent need for therapies with an improved balance between antiarrhythmic efficacy on one hand, and tolerability and safety on the other.'' *Sanofi and Sanofi-Aventis v. Glenmark Pharmaceuticals, Inc*., Civil Action No. 14-264-RGA (Consolidated), Aug. 31, 2016, (D. Del. 2016). The facts clearly established that no other AAD had been demonstrated to reduce both cardiovascular and atrial fibrillation hospitalizations, nor had an additional drug been developed since. The favorable properties of dronedarone were directly attributed to the structure of the molecule which was the subject of the claims at issue.

The type of claim may play an important role in determining whether the assertion of an unmet need is satisfied. The previous examples were all composition of matter claims to a small organic molecule. US 6,284,770 claimed a method for treating irritable bowel syndrome (specifically with alosetron) rather than claiming the small molecule itself. *Prometheus Laboratories v. Roxane Laboratories*, 805 F.3d 1092 (Fed. Cir. 2015). Alosetron is marketed under the tradename Lotronex® by Prometheus Laboratories for the treatment of irritable bowel syndrome in women. It was originally developed by GlaxoSmithKline before being removed from the market due to serious adverse side effects. It was eventually reintroduced with additional safety precautions and warnings. Importantly, the only special instructions related to the method of treatment for patients with irritable bowel syndrome were an assessment by a physician of the symptoms and condition of the patient. Prometheus introduced evidence of a long felt need for the treatment of severe irritable bowel syndrome, but the court found it unpersuasive. The District Court held, and the Federal Circuit affirmed, that ''any praise or reduction in the severity of side effects is more likely attributable to elements from the [composition of matter] patent, the new safety precautions, heightened awareness, and warnings issued after Lotronex's reintroduction.'' *Id.* at 1102. Importantly, the court agreed that while there may have been a long felt and unmet need for improved treatments for irritable bowel syndrome, it attributed meeting that need to the small molecule itself rather than to the method of treatment covered in the patent. *Id.* The small-molecule was covered in a different patent as a composition of matter.

Ertapenem is marketed under the tradename of Invanz® by Merck for the treatment of both gram-negative and gram-positive bacterial infections. In another instance where the court was unpersuaded regarding the evidence of an unmet need, US 5,952,323 claimed a stable formulation for ertapenem. *Merck Sharp & Dohme Corp. v. Hospira*, Civil Action No. 14-915-RGA, (Del. 2016). The claims were for a specific stable formulation of ertapenem rather than for ertapenem itself. The court held that while the stable formulation might be required for commercial success, it was not required for commercial availability. Additionally, because there were other antibiotics on the market that were used for the same types of infections, evidence supporting an unmet need was not persuasive. Improved administration and an improved safety profile as compared to other antibiotics on the market did not support an unmet need. The court emphasized that there must be a ''nexus between the evidence and the merits of the claimed invention.'' *Merck Sharp & Dohme*, Civil Action No. 14-915-RGA, citing *In re GPAC, Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995).

The same issues regarding secondary conditions that apply to small molecule drugs also apply to pharmaceutical devices. US 5,989,581 covers NuvaRing®, a contraceptive medical device marketed by Organon USA and Merck Sharp & Dohme, suitable for vaginal insertion that releases a combination of progestogenic and estrogenic compounds in an amount suitable to prevent pregnancy. Merck presented evidence that there was a long-felt and unmet need for hormonal birth control that could be administered once every 28 days, could be inserted and removed by the patient, could not be seen, did not irritate the patient and was readily reversible. *Merck Sharp & Dohme Corp. v. Warner Chilcott,* Civil Action No. 13-2088-GMS (Del. 2016). While all of these assertions may or may not be true (and the court did not opine on that issue), the court concluded that those features and what was inventive with the device were not claimed in this patent. The claims were directed at a device comprising the two drugs and the manner in which the drugs were entrained in a combination of thermoplastic polymers thereby permitting slow release over the targeted time period. The court emphasized that ''[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision.'' *Merck Sharp & Dohme,* Civil Action No. 13-2088-GMS citing *Muniauction, Inc. v. Thomson Corp*., 532 F.3d 1318, 1327 (Fed. Cir. 2008) (alteration in original) (quoting *Ruiz v. A.B. Chance Co*., 234 F.3d 654, 668 (Fed. Cir. 2000)).

The key takeaways from this are that the analysis for a long felt and unmet need is very fact-specific. Support must be easily understood and not subject to alternative interpretations. As the court said in rejecting assertions of a long felt and unmet need, there must be a direct nexus between the evidence presented and the claims. Limitations in the specification are not read into the claims. Manual of Patent Examining Procedure § 2173.01(I) citing *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). Instead, the claims must stand on their own. Courts are willing to separate a small molecule from its formulation and method of administration, so a drug's therapeutic properties may be more readily supported as meeting a long-felt and unmet need. Support in the non-patent and peer reviewed literature from numerous independent authors is extremely strong and difficult to refute.

- Failure of Others

The failure of others as a secondary consideration is closely related to a long-felt and unmet need with the rationale that a company wouldn't attempt to develop a product in the face of the failure of others unless there was a strong need for that product. *Cyclobenzaprine Hydrochloride* 676 F.3d at 1082 and references cited therein. Cyclobenzaprine hydrochloride is marketed under the tradename of Amrix® as a skeletal muscle relaxant by Pharmatech, Inc., a wholly owned subsidiary of Cephalon, Inc. During ANDA litigation, the Federal Circuit overturned the District Court when it held that the evidence supporting the failure of others ''strong[ly] supports a nonobviousness finding.'' *Id.* at 1081. Testi-

mony was presented at trial from the CEO of a competing company that had tried and failed to commercialize cyclobenzaprine hydrochloride. The District Court disregarded this evidence because testimony established that the competing company was attempting to develop a therapeutically effective product having fewer side effects while Pharmatech and Cephalon were just attempting to develop a marketable product. The Federal Circuit found clear error in the District Court's decision disregarding this evidence and overturned the lower court's narrow interpretation of the goal suggesting that both companies were trying to bring a product to market. As the Federal Circuit noted, the claims of the patent were only directed to a formulation that was therapeutically effective, not at a formulation that was therapeutically effective and had fewer side effects. *Id.* The addition of a second goal did not negate the common goal between the two companies, and there was a clear nexus between the claims and the evidence. The court also noted that the same arguments supporting the failure of others is strong support that there is no reasonable expectation of success. *Id*. at 1081 citing *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1354 (Fed. Cir. 2003).

During the development of olanzapine, Eli Lilly presented strong evidence regarding the failure of others to bring to market a replacement for clozapine to treat schizophrenia and bipolar disorder. *Eli Lilly & Co.*, 364 F. Supp.2d at 820 affirmed in *Eli Lilly & Co.*, 471 F.3d at 1369. Testimony illustrated how closely the long-felt need tied to the failure of others. The Findings of Fact included an article from a prominent peer-reviewed medical journal stating that ''[d]espite the extensive developmental effort in this area, no alternative to clozapine has been identified that has clinical antipsychotic efficacy and no extrapyramidal neurologic side effects, but has a low risk of inducing other important toxic effects (bone marrow suppression or seizures).'' *Eli Lilly & Co*., 364 F. Supp.2d at 832, fact 23. Eli Lilly also illustrated their own work over more than 20 years, including failed clinical trial data, to develop a product that would be safer and more effective than clozapine. *Id.* at 832 – 834, facts 25 to 39.

In addition to establishing a long felt and unmet need, dronedarone illustrates how the failure of others can support a determination of nonobviousness. *Sanofi and Sanofi-Aventis*, Civil Action No. 14-264-RGA. The prior art illustrated numerous failed clinical trials due to inconsistent results for AADs in general and dronedarone specifically. The court determined that ''in light of dronedarone's less than stellar track record in clinical trials before [the successful clinical trial] and the historical uncertainty surrounding antiarrhythmic drugs, I find it much more likely that a [person of skill in the art] would be considerably skeptical of dronedarone's ability to actually succeed in reducing the risk of cardiovascular hospitalization and hospitalization due to [atrial fibrillation].'' *Id.* The court found it not credible that a person of ordinary skill in the art would be able to look at two decades of erratic clinical trial results and be able to extrapolate a path to a successful trial as asserted by the defendant. The data may have provided a motivation to continue development of dronedarone, but it did not support any reasonable expectation of success in light of the repeated failures. *Id.*

Oxycodone is marketed under the tradename OxyContin® by Purdue Pharmaceuticals for the treatment of moderate to severe pain. In a case where the court found that the evidence did not support the conclusion of a failure of others, Purdue Pharmaceuticals argued that the formation of oxycodone having a low concentration of an undesirable impurity (abbreviated as ''ABUK'') supported the conclusion of nonobviousness. *In re Oxycontin Antitrust Litigation* and *Purdue Pharma v. Teva Pharmaceuticals*, 994 F. Supp.2d 367 (S.D. NY 2014) affirmed in *Purdue Pharma v. Teva Pharmaceuticals*, 811 F.3d 1345 (Fed. Cir. 2016). The court found that despite Purdue's assertion that the undesirable impurity was known several years before the development of low-ABUK oxycodone and that nobody had successfully developed a low-ABUK oxycodone product, there was no evidence that others had tried to produce one. On the contrary, the evidence suggested that when the U.S. FDA informed the manufacturer that it was necessary to produce low-ABUK oxycodone, the supplier was able to provide it on the agreed upon timetable of less than one year. *Id.*at 994 F. Supp.2d at 401 and 811 F.3d at 1355.

Ertapenem litigation provides another example where the court was unpersuaded regarding the failure of others. Merck argued that because ertapenem was initially discovered by Zeneca but later licensed to Merck for development, it must mean that Zeneca tried and failed to produce a stable formulation that would be suitable for market. The court found that this was too speculative because ''[t]here are many reasons why a company might not choose to undertake the process of taking an active pharmaceutical ingredient and developing a final formulated product.'' *Merck Sharp & Dohme Corp. v. Hospira*, Civil Action No. 14-915-RGA, Dist. Del. 2016 at § 3. There was no evidence as to why Zeneca licensed the patent to Merck, or that suggested a failed attempt to find a stable and marketable formulation for ertapenem.

The key takeaway from this is that clear evidence is required to support a conclusion that others have tried and failed to address a known problem. Knowing there is a problem and attempting to solve it are different issues, and evidence supporting one does not necessarily support the other. Additionally, evidence that will support the conclusion of a long felt and unmet need may provide similar support to the conclusion that others have tried and failed to solve a known problem. As a corollary to *In re Gershon*, if someone is the first to recognize a problem, in addition to not supporting the conclusion that there is a long-felt and unmet need, there is probably no evidence to support the conclusion that others have tried and failed to solve a problem.

■ Unexpected Results or Properties

Both the structure and properties of a small molecule may be considered in relation to unexpected results or properties in an obviousness analysis.

''From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared.'' *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963).

Eli Lilly presented strong evidence of unexpected results for olanzapine. Olanzapine is a homolog of another compound (referred to as compound 222) prepared by replacing an ethyl group in compound 222

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with a methyl group to make olanzapine. Homologs are defined as molecules that are structurally closely related compounds only differing by the successive addition of the same chemical group. For example, one common series of homologous substitutions in a molecule is methyl, ethyl, propyl and butyl. These are different than ''isomers'' which have the same chemical formula but a different arrangement of atoms. Isomers may or may not be structurally similar and are analyzed differently. Because of the structural similarity between homologs, they often have similar physiological properties and are frequently rejected under the theory that it would be obvious to try to make them and have a reasonable expectation of success. MPEP § 2144.09(I) citing *In re Payne*, 606 F.2d 303, 313, (CCPA 1979). In an *in vivo* dog study comparing compound 222 to olanzapine, Eli Lilly illustrated a significant difference in the biological activity between the two molecules. Compound 222 caused an increase in the serum cholesterol level of dogs while olanzapine did not. There was also no difference in the blood serum cholesterol level between olanzapine and the control group that received a placebo. This was both unexpected and surprising. An additional study commissioned by Zenith confirmed this conclusion and revealed that the increase of the bad cholesterol (LDL cholesterol) was six times greater than the increase in the good cholesterol (HDL cholesterol). Despite criticism of the use of an *in vivo* dog model for these studies, the court held that the results were scientifically sound and found credible testimony that established ''a known and reported nexus between dog studies and humans with regard to total cholesterol.'' *Eli Lilly & Co.*, 364 F. Supp.2d at 857 – 858, facts 222 to 229. Expert testimony and peer-reviewed literature established that ''dogs proved to be a reasonable predictor of cholesterol effects in humans in that statins decrease cholesterol in both dogs and humans.'' *Id.* at 857, fact 222. While the Federal Circuit did not elaborate on the discussion of unexpected results from the District Court, it found that ''these objective criteria buttressed the trial court's conclusion of nonobviousness.'' *Eli Lilly & Co.*, 471 F.3d at 1380.

While Merck was not able to convince the court regarding the failure of others in the development of ertapenem, they were able to show unexpected results. *Merck Sharp & Dohme*, Civil Action No. 14-915-RGA. While working to develop a stable formulation for the antibiotic, they observed that ertapenem formed dimers in solution that interfered with both activity and stability. The inventors added sodium bicarbonate to the formulation to function as an inert buffer but discovered that the carbonate added to the molecule to form a stable carbamate. Although this adduct was not unexpected, the stabilizing effect was. Prior art literature established that these kinds of adducts with similar molecules were ''known to cause degradation.'' *Id.* at § 4. While the court found that these adducts may inherently form, ''[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.'' *Id.* at § 4 citing *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966).

In a case where the court ultimately found that the evidence of unexpected results was not persuasive, the court made an important observation in regards to pharmaceutical development. *Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007). A significant percentage of small molecule drugs are marketed as salts rather than as free bases or acids. A common guide to developing a salt form is an article by Berge regarding pharmaceutically acceptable salts. S. M. Berge, L. D. Bighley, D. C. Monkhouse, ''Pharmaceutical Salts,'' *J. Pharm. Sci.*, 66(1),1-19 (Jan. 1977). Many patents and patent application specifically reference this article when they define a ''pharmaceutically acceptable salt'' in the specification (Note: a search conducted in January 2017 on PaFT of published patent applications for ''Berge'' and ''Pharmaceutical Sciences'' had over 7000 hits).

During ANDA litigation regarding amlodipine besylate, sold under the tradename Norvasc® for the treatment of hypertension and chronic stable and vasospastic angina, Pfizer presented evidence that the besylate salt of amlodipine was superior to the mesylate salt and several other salts because of superior stability and processing. *Pfizer,* 480 F.3d at 1348. It was well known in the art that different salt forms may exhibit differences in a variety of properties, including, but not limited to solubility, stability, hygroscopicity and stickiness. Pfizer asserted that the superior properties ''have significant practical value and are indicative of nonobviousness.'' *Id.* at 1370. The Federal Circuit, in overturning the District Court, agreed that the results may have been superior to other salts of amlodipine, but the District Court's conclusion was clear error because ''any superior property must be unexpected to be considered as evidence of non-obviousness.'' *Id.* at 1371 citing *In re Chupp*, 816 F.2d 643, 646 (Fed.Cir.1987). Most importantly:

''Pfizer's evidence must fail because the record is devoid of any evidence of what the skilled artisan ***would have expected***. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. . .The district court wrongly relied on the fact that the 'besylate salt works' because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life (emphasis added).'' *Pfizer,* 480 F.3d at 1371.

Optimization of the salt form was called ''routine experimentation'' and ''obvious to try'' because Berge provides a list of 53 different pharmaceutically acceptable salts, and it is well known in the art that different salts often have different properties. *Id.* Just because one salt has better formulation properties than another is not enough to support the conclusion of unexpected results. ''When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.'' *Id.* at 1371 citing *In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir.1991).

During litigation over oxycodone, Purdue Pharmaceuticals presented evidence suggesting that certain impurities were unexpected and that the method of making low-ABUK oxycodone was unexpected. *Oxycontin Antitrust Litigation*, 994 F. Supp.2d at 367 affirmed in *Purdue Pharma*, 811 F.3d at 1345. However, the claims in the patent were not for the process of making the low-ABUK oxycodone. The patent claimed an improved formulation that comprised low-ABUK oxycodone, not its method of preparation. Additionally, the court held that while ''the existence of [an impurity] was unexpected, the properties of [the impurity] were not unex-

pected.'' *Oxycontin Antitrust Litigation,* 994 F. Supp.2d at 401. Expert testimony established that the chemistry was well understood by a person having ordinary skill in the art so that the structural differences between the impurity and the target molecule would allow ''a skilled artisan to 'make a confident prediction about the relative reactivities' '' of the two molecules. *Id.*

There are a couple of significant takeaways from this. First, when arguing that results are unexpected in a patent, it is important to remember that ''objective evidence of nonobviousness must be commensurate in scope with ***the claims*** which the evidence is offered to support (emphasis added).'' *In re Clemens*, 622 F.2d 1029, 1036, (CCPA 1980). Suggesting that a property or result is unexpected is only effective if that property or result is claimed. Additionally, there must be a point of reference for the comparison of the unexpected results. There is nothing unexpected in a result in and of itself. All research produces results, even if they are negative results. There must be a basis for comparison that makes the results surprising or unexpected, and that basis must be part of the evidence.

■ Skepticism of Experts

Skepticism of experts in regard to a specific line of research or the viability of a method of treatment is significant because it serves to discourage researchers from pursuing that line of investigation. ''The skepticism of an expert, expressed ***before*** these inventors proved him wrong, is entitled to fair evidentiary weight (emphasis added).'' *In re Dow Chemical Co*., 837 F.2d 469 (Fed. Cir. 1988).

Rosuvastatin calcium, marketed under the tradename of Crestor® by AstraZeneca for the treatment of high cholesterol and fats (triglycerides) in the blood and used to reduce the incidence of heart disease and stroke, was the subject of a significant amount of ANDA litigation as multiple generic manufacturers attempted to market a generic product. *In re Rosuvastatin Calcium Patent Litigation*, 719 F. Supp.2d 388 (D. Del. 2010) affirmed in *In re Rosuvastatin Calcium Patent Litigation,* 703 F.3d 511 (Fed. Cir. 2012). Structurally, rosuvastatin is similar to competing products which could serve as a ''lead compound'' in developing a new, noninfringing product. Testimony from three experts established that there was ''much skepticism in the industry concerning the safety of rosuvastatin. . .and the Court finds it telling that no other pharmaceutical companies attempted to create a comparable product despite research in the area and the economic incentives of entering an additional player in the statin market.'' *In re Rosuvastatin*, 719 F. Supp.2d at 407. Significantly, the Federal Circuit wrote ''[w]e agree that 'obvious to try' was negated by the general skepticism concerning pyrimidine-based statins, the fact that other pharmaceutical companies had abandoned this general structure, and the evidence that the prior art taught a preference not for hydrophilic substituents but for lipophilic substituents at the C2 position.'' *In re Rosuvastatin,* 703 F.3d at 518.

Omeprazole, marketed under the tradenames of Zegerid® and Prilosec® and originally developed by AstraZeneca for the treatment of ulcers and excess stomach acid (also known as heartburn), has been the subject of much ANDA litigation over the years, including the small molecule, multiple formulations and methods of treatment. In this particular case, a specific formulation of omeprazole was claimed. *Santarus v. Par Pharmaceuticals*, 720 F. Supp.2d 427 (D. Del. 2010) affirmed in part *Santarus v. Par Pharmaceuticals*, 694 F.3d 1344 (Fed. Cir. 2012). Expert testimony was presented regarding skepticism that the patents encompassed ''a long-held belief that buffered approaches were unworkable and that enteric coating was essential for solid dosage forms'' of omeprazole. *Santarus*, 720 F. Supp.2d at 456. Several reasons were given by the court in finding the testimony unpersuasive. First, the statement from the expert was read into the record rather than presented live and subject to cross-examination. Because of this, the factfinder could give no context to the statements made by the expert. Second, the timing of the statements was suspect and reduced their impact. They were made nearly 20 years after the initial research into omeprazole, eight years after the patents at issue were filed, and one year after the patents were issued. Lastly, the statements were made at an investor's symposium for a company which the expert was consulting rather than at a conference of scientific professionals or in a peer-reviewed journal. *Id.* The District Court found the testimony unavailing, and the Federal Circuit deferred to these factual findings because they were not clearly erroneous. *Santarus*, 694 F.3d at 1358.

In an unusual instance involving a pharmaceutical device, the District Court found, and the Federal Circuit affirmed, that the skepticism of experts can arise post-patenting rather than pre-patenting. *Pressure Products Medical Supplies, Inc. v. Greatbatch Ltd.*, 599 F.3d 1308, (Fed. Cir. 2010) (affirmed in part, reversed in part and remanded). Pressure Products sued for alleged infringement on a device that enabled a surgeon to place and remove catheters or pacemaker leads into a blood vessel while enabling blood flow regulation during the operation. The evidence showed that multiple other medical device manufacturers turned down the chance to license the device because ''they did not believe it would work.'' *Id.* at 1319. Although the court did not say it, the conclusion was that that the potential licensees of the patent holder would be considered experts whose opinion would have evidentiary value.

The key takeaway from this is that for the skepticism of experts to be persuasive to a court, it cannot be clearly self-serving for the patent holder. A judge will look closely at the motivation of the expert and the nature of the alleged skepticism. Statements in a scientific forum will carry much more weight than a statement outside of that context. In some circumstances, the skepticism can arise after a patent application is filed, but this is unusual.

Conclusion for Part One This ends Part One on the use of secondary considerations in pharmaceutical patents and litigation. While the evidentiary requirements for long-felt need, failure of others, and skepticism of others are different, they often overlap. One can easily lead to another which in turn leads to the third. For unexpected results, it is important to have a baseline comparison as to what was expected so that the unexpected nature of the result has a basis for comparison. Conclusory statements are not enough.

In Part Two, post-patenting secondary considerations will be examined. These include commercial success, praise by others, copying by others and simultaneous invention. While they can often support a conclusion of nonobviousness, there are situations where the evidence can lead to the exact opposite conclusion.

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