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Secondary Considerations in Pharmaceutical Patents: Part Two

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Introduction and Background

This is Part Two of a pair of articles regarding secondary considerations of nonobviousness in pharmaceutical patents. Part One (published in the Feb. 3, 2017, issue of *Pharmaceutical Law & Industry Report* (15 PLIR 183, 2/3/17)) examined the pre-patenting secondary considerations of long-felt need, failure of others, unexpected results, and skepticism of experts and the evidence needed to support a determination of nonobviousness under 35 U.S.C. § 103. Part Two examines the post-patenting secondary considerations of commercial success, praise by others, copying by others, and simultaneous invention.

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The post-patenting secondary considerations present a different set of issues in regard to the evidentiary requirements and their interpretation. When present, all of the pre-patenting secondary considerations support a conclusion of nonobviousness; however, three of the four post-patenting secondary considerations have the possibility of providing little support or of becoming a negative factor in support of patent validity under 35 U.S.C. § 103. Additionally, due to the unique requirements of bioequivalence imposed under the Hatch-Waxman Act, copying a marketed product by a putative generic manufacturer may or may not support a conclusion of nonobviousness.

As discussed in Part One, obviousness rejections under 35 U.S.C. § 103 are probably the most subjective of all rejections received during the prosecution of a patent, but they are also one of the most common. Analysis of the four *Graham* factors is done to determine whether or not an invention is obvious, and secondary considerations are supposed to play an important role in the final determination. *Graham v. John Deere*, 383 U.S. 1 (1966). While the first three factors in a *Graham* analysis are relatively straightforward, it is the issue of secondary considerations that creates difficulty for courts, examiners and attorneys alike.

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.

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§ 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. With that in mind, an analysis and discussion of the post-patenting secondary considerations is presented.

Post-Patenting Secondary Considerations Post-patenting secondary considerations include commercial success, praise by others, copying by others and simultaneous invention. Unlike the pre-patenting secondary considerations, they are seldom available during prosecution of the patent. In most cases, these secondary considerations will be argued during infringement litigation, a Post-Grant Proceeding or, rarely, a reissue proceeding. As such, this evidence will be introduced by either declaration or testimony from a properly qualified individual. The type of expert or witness must be carefully selected to provide testimony that clearly supports nonobviousness while simultaneously being readily understood by the factfinder. Regardless of how the evidence is introduced, understanding what evidence is and isn't persuasive is critical in convincing the court or Patent Trial and Appeal Board to uphold the validity of a patent against an assertion of invalidity under 35 U.S.C. § 103.

■ Commercial Success

One important post-patenting indicia of nonobviousness is the commercial success of a product.

''Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious.'' *Merck & Co., Inc. v. Teva Pharmaceuticals USA*, 395 F.3d 1364,1376 (Fed. Cir. 2005) paraphrasing *Graham v John Deere Co.*, 383 U.S. 1, 17 – 18 (1966).

The successful product must be embodied in the claims of the patent. *Rolls-Royce, PLC v. United Tech. Corp.,* 603 F.3d 1325, 1340 (Fed.Cir. 2010). ''[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.'' *Teva Pharmaceuticals USA v. Sandoz, Inc*, 876 F. Supp.2d 295, 416 (S.D. N.Y. 2012) citing *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.,* 229 F.3d 1120, 1130 (Fed.Cir. 2000). In other words, the claims in the challenged patent must embody the marketed product; claims to a method of use of a composition (e.g., a dosing regimen or pharmacokinetic profile) may or may not be coextensive with the claims and important for the commercial success of the marketed product. Likewise, a liquid or intravenous formulation does not embody a tablet or capsule for oral administration. Furthermore, the exclusivity granted during the life of a patent may either negate entirely or reduce the evidentiary value of a showing of commercial success.

Glatiramer acetate, marketed under the tradename of Copaxone® by Teva Pharmaceuticals for the treatment of multiple sclerosis has been the subject of numerous ANDA lawsuits. In this suit Teva Pharmaceuticals introduced strong evidence illustrating the commercial success of their marketed product. *Teva Pharmaceuticals USA v. Sandoz, Inc*, 876 F. Supp.2d 295, (S.D. N.Y. 2012) affirmed-in-part in *Teva Pharmaceuticals USA v. Sandoz, Inc*, 723 F.3d 1363 (Fed Cir. 2013). Sales exceeded $10 billion ''despite constant pressure from competitors.'' *Teva Pharmaceuticals*, 876 F. Supp.2d at 416. Importantly, the court found that the marketed product was co-extensive with the claims at issue. Because of that finding, the nexus between the sales information and the product was presumed. The defendants failed to prove that the commercial success was due to extraneous factors, such as marketing or advertising. ''[I]t is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors. . .[A]rgument and conjecture are insufficient.'' *Teva Pharmaceuticals*, 876 F. Supp.2d at 416 – 417 citing *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed.Cir.1988).

Enrofloxacin, marketed under the tradename of Baytril® by Bayer for the treatment of infections in companion and farm animals, illustrates an unusual instance where a method of treatment was successfully shown to have a nexus to the commercial success of the product. *Bayer Healthcare v. Zoetis, Inc.,* No. 12 C 00630 (Aug. 6, 2016, N.D. Ill.). Pfizer sought to invalidate US 5,756,506 that claimed a method of treating bacterial infections in animals with a single dose of a fluoroquinolone – a class of antibiotics long established for the treatment of a variety of bacterial infections, including some resistant infections. (Note: Zoetis, Inc. was spun out of Pfizer and became the named defendant. The opinion stays with the name of Pfizer because exhibits and briefs were initially written under that name). Notably, Bayer did not claim the fluoroquinolone composition because these were already well-known. Bayer marketed a solution of enrofloxacin, a fluoroquinolone discovered many years earlier, with specific instructions for its use (a single high dose). A competing fluoroquinolone from Pfizer was on the market having a similar effect except it required a different treatment regimen (at least two doses). Pfizer admitted in marketing seminars that the reason that Baytril® commanded a 94 percent market share was due to the fact that it was single-dose administration rather than multiple-dose administration: ''[p]roducts that do not work in a single-dose regimen are not really practical in today's environment.'' *Bayer Healthcare,* No. 12 C 00630 at § IV(B)(2)(iii). Pfizer was only able to present conclusory statements that the claimed method was ''untethered to the actual invention.'' *Id.*

The commercial success of a pharmaceutical product, when there is a nexus between the claimed invention and the commercial success, can provide invaluable evidence of nonobviousness as long as ''the sales were a direct result of the unique characteristics of the claimed invention.'' *Merck Sharp & Dohme Corp. v. Hospira*, Civil Action No. 14-915-RGA, (D. Del. 2016) citing *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). However, in an unusual twist of patent law, the commercial success

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of a product may not be given much weight in a nonobviousness analysis.

Ertapenem is marketed under the tradename Invanz® by Merck for the treatment of both gram-negative and gram-positive bacterial infections. During ANDA litigation, the District Court agreed that its stable formulation was a commercial success. *Merck Sharp & Dohme Corp. v. Hospira*, Civil Action No. 14-915-RGA, (D. Del. 2016). Testimony established that the market share of Invanz® continuously increased reaching over $3.25 billion worldwide despite the fact that there were several competing products. Prior to developing a stable formulation of ertapenem, the molecule was known to be unstable requiring storage at -20°C. Additionally, it was unstable in solution and decomposed too quickly for administration in a hospital. *Id.* But for the formulation developed by Merck, there would have been no marketable product. All of these factors contributed to the commercial success of ertapenem. However, despite the fact that there was a clear nexus between the marketed product and the claims, the evidence of commercial success was considered weak. No other company was permitted to develop ertapenem due to another patent. Because ''market entry by others was precluded [due to patent protection and statutory exclusivity], the inference of non-obviousness. . .from evidence of commercial success. . .is weak.'' *Merck Sharp & Dohme*, Civil Action No. 14-915-RGA citing *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Procter & Gamble had a similar result with risedronate, sold under the tradenames of Actonel®, Atelvia® and Benet® and originally developed by Warner Chilcott for the treatment of osteoporosis, when they presented strong evidence of the commercial success. *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). It had undisputedly become a blockbuster drug generating annual sales of over $2.7 billion; however, this evidence was found to be of little probative value because of a prior art patent. The court determined that the closest prior art was another patent assigned to Procter & Gamble, so any possible competitors were precluded from developing a similar drug. The District Court held, and the Federal Circuit affirmed, that the commercial success was not due to the patentable features of the molecule; it was due to market exclusivity. ''Where the relevant community is blocked from acting on the prior art, the inference of nonobviousness from evidence of commercial success is weak.'' *Procter & Gamble* 536 F. Supp.2d at 497 citing *Merck & Co., Inc. v. Teva Pharmaceuticals, USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Oxycodone is marketed under the tradename OxyContin® by Purdue Pharmaceuticals for the treatment of moderate to severe pain. During litigation Purdue Pharmaceuticals argued that the commercial success of the product was strong evidence of nonobviousness. *In re Oxycontin Antitrust Litigation* and *Purdue Pharma v. Teva Pharmaceuticals*, 994 F. Supp.2d 367 (S.D. N.Y. 2014) affirmed in *Purdue Pharma v. Teva Pharmaceuticals*, 811 F.3d 1345 (Fed. Cir. 2016). Purdue's expert testified that the fact that there was over $2 billion in sales of the marketed product was strong evidence of commercial success; however, this analysis failed to show a nexus to the claims in the patent. The claims were directed to a formulation of oxycodone having a low concentration of an undesirable impurity (abbreviated as ''ABUK''). The court found that there was no nexus between the commercial success of OxyContin® and the low-ABUK formulation in part because Purdue never marketed this feature to the public. The supplier of the low-ABUK oxycodone, a corporate affiliate of Purdue Pharmaceuticals, had attempted to find additional purchasers for their material but were unable to do so. Their only sales of the low-ABUK oxycodone were to their own affiliated company, so the court found that, despite significant sales, there was no commercial success. Additionally, the specific formulation of oxycodone was reintroduced and remarketed in a tamper resistant formulation after the original product was removed from the market. Comparison of the sales data from before the product was removed from the market to the newly introduced product did not support a nexus of the claims to the commercial success. No increased sales or increased price was present in the new formulation compared to the original formulation leading the court to conclude that the sales data was not tied to the claims. *In re Oxycontin Antitrust Litigation*, 994 F. Supp.2d at 427. Expert testimony stated simply that the fact that there was over $2 billion in sales meant that the drug was ''quite successful.'' No comparison or analysis was presented in regard to the market in which the drug competed or to other opiates, so this testimony was ''not useful to the Court.'' *In re Oxycontin Antitrust Litigation*, 994 F. Supp.2d at footnote 11.

There are a couple of key takeaways here. First, there must be a clear nexus between the marketed product or method and the claims. A court will look closely to ensure that the claims are directed to the marketed product rather than an ancillary aspect of it. Second, patent exclusivity can be a double-edged sword. It can provide market exclusivity for a product thereby allowing for commercial success, but can also diminish the evidentiary value of commercial success in an obviousness determination. Establishing that there are competitors to a marketed product is important when a patent provides broad-ranging protection. If nobody is able to compete with a product, then the limited exclusivity provided by the patent may be the cause of the commercial success rather than the product itself. Finally, commercial success in the marketplace does not mean commercial success under 35 U.S.C. § 103. They are two very different issues, and evidence of one may or may not support the other.

- Praise by Others

Olanzapine is sold under the trade name of Zyprexa® and was first marketed by Eli Lilly as an atypical antipsychotic for the treatment of schizophrenia and bipolar disorder. It is a classic example of how praise by others, sometimes referred to as industry acclaim or industry recognition, can provide strong support of nonobviousness. *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). The company and the inventor received numerous awards in regard to the development of an improved treatment for certain psychotic disorders. Testimony from doctors who prescribed the drug along with patients who took it was introduced attesting to its efficacy and improved biological profile. The Defendant argued that a competing product (risperidone) received

some of the same awards at different times, so the evidence of nonobviousness should receive little weight. The District Court was unpersuaded and found that an award directed at a competing product ''does not vitiate the industry acclaim held by olanzapine.'' *Eli Lilly & Co*, 364 F. Supp.2d at 853 (Findings of Fact § 198). The District Court found, and the Federal Circuit affirmed, that this evidence, along with additional evidence regarding other secondary considerations, ''buttressed the trial court's conclusion of nonobviousness.'' *Eli Lilly & Co.*, 471 F.3d at 1380. ''Appreciation of the invention by those of ordinary skill in the art is further evidence that the invention would not have been obvious (citations omitted).'' *Eli Lilly & Co*, 364 F. Supp.2d at 907 (Conclusions of Law § 91 – 93).

Dronedarone, marketed under the tradename of Multaq® by Sanofi-Aventis as an antiarrhythmic drug (AAD), illustrates another important point. The praise and recognition for a pharmaceutical product can occur before it receives marketing approval from the U.S. Food and Drug Administration (FDA). During ANDA litigation over dronedarone, claim 1 of US 8,410,167 was directed at ''[a] method of decreasing a risk of cardiovascular hospitalization in a patient. . .'' *Sanofi and Sanofi-Aventis v. Glenmark Pharmaceuticals, Inc.*, Civil Action No. 14-264-RGA (Consolidated), Aug. 31, 2016, (D. Del. 2016). Shortly after the initial clinical trial results were released, testimony established that multiple sources praised the treatment as ''remarkable'' and ''groundbreaking'' because of the significant reduction in hospitalization. *Sanofi,* Civil Action No. 14-264-RGA (Consolidated), at *21, ¶ 1.This evidence was further supported with evidence showing inconsistent clinical trial results for drugs in the same class for the same medical condition.

On the other hand, praise by others does not always provide the required nexus to the claims. NuvaRing®, a pharmaceutical device marketed by Organon USA and Merck Sharp & Dohme, is a once monthly contraceptive pharmaceutical device suitable for vaginal insertion that releases a combination of progestogenic and estrogenic compounds in an amount suitable to prevent pregnancy. Despite extensive industry recognition, including *Time Magazine*'s Best Innovation of the Year for Health award, the District Court found that the required nexus between the claims and the product was not present. *Merck Sharp & Dohme Corp. v. Warner Chilcott,* Civil Action No. 13-2088-GMS (D. Del. 2016). The claims were directed to the manner in which the two drug combination was entrained in the device using a combination of thermoplastic polymers that allowed for extended release of the antigestagenic compounds. The awards and industry recognition were directed at the device itself and the unmet needs that it satisfied. ''It may have taken 'almost 30 years of industry efforts' to bring such a ring to the market (D.I. 140 at 37), but these advantages and long-felt need are not what is inventive in the '581 patent. Because there is no relationship between the inventive features and industry recognition or long-felt need, they do not weigh in favor of a finding of non-obviousness.'' *Id.* at § V(4)(ii).

The key takeaway here is the requirement for a nexus between the claims and the praise directed at the product. As with other secondary conditions, a court will look closely to ensure that the praise is not due to factors not claimed. The aspects of the product that receive the praise or awards must be claimed. It is also important to remember that not all praise for a product has to come after FDA approval. The entire timeline for a product should be examined.

■ Copying by Others

As Oscar Wilde said, ''imitation is the sincerest form of flattery that mediocrity can pay to greatness.'' While it may not be the ''sincerest'' in the legal sense, it can provide valuable evidence of nonobviousness. In the context of ANDA litigation, it is important to remember that copying of the active pharmaceutical ingredient (API) by a putative generic manufacturer is not considered copying in regards to an obviousness determination under 35 U.S.C. § 103. The generic manufacturer is statutorily obligated to copy the API and establish ''that the new drug is bioequivalent to the listed drug. . .'' 21 U.S.C. § 355(j)(2)(A)(iv), *et seq*. While that would seem to preclude the possibility of copying during ANDA litigation, the issue is not so clear. ''The copying of an invention may constitute evidence that the invention is not an obvious one. This would be particularly true where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed.'' *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed.Cir.1984). A recently published article has focused extensively on just this issue: ''Copying as Objective Evidence of Non-Obviousness in ANDA Cases is Alive and Well,'' *Pharmaceutical Law & Industry Report*, 15 PLIR 73 (January 13, 2017) by B. R. Rudolph and R. C. Stanley.

During ertapenem ANDA litigation, Merck presented evidence that the formulation developed by Hospira was identical to that embodied by the Merck patents and the marketed product. *Merck Sharp & Dohme*, Civil Action No. 14-915-RGA. They were also able to show that Hospira worked to develop a different formulation of the antibiotic using different excipients and stabilizers in an attempt to avoid the Merck patents. In finding that there was evidence of copying, the District Court wrote that ''[t]he generic is not, however, required to copy the inactive ingredients or the methods used in a manufacturing process.'' *Merck Sharp & Dohme,* Civil Action No. 14-915-RGA at § I(B)(iii)(c)(2) citing *Dey, L.P. v. Teva Parenteral Meds., Inc.*, 6 F. Supp.3d 651, 681 (N.D. W.Va. 2014). The court did not address the issue as to whether or not the excipients and stabilizers were required for bioequivalence but focused instead on the attempts by Hospira to design around the patented formulation.

During ANDA litigation over an extended release formulation of tramadol hydrochloride, marketed under the tradename Ultram ER® by Purdue Pharmaceuticals for the treatment of pain, the District Court came to the opposite conclusion. *Purdue Pharma Products v. Par Pharmaceutical, Inc.,* 642 F. Supp.2d 329, 373 (D. Del, 2009). Purdue presented evidence showing that Par's formulation was ''virtually identical'' and that the Par scientists has studied the Purdue patents. The court held, and the Federal Circuit affirmed in a non-precedential decision (*Purdue Pharma Products v. Par Pharmaceutical, Inc.,* Nos. 2009-1553, 2009-1592 (Fed. Circ. 2010, non-precedential)), that:

''a showing of copying, which Plaintiffs have provided here. . .is not compelling evidence of non-obviousness in the Hatch-Waxman context. . .'[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to

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assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective.' '' *Purdue Pharma*, 642 F. Supp.2d at 374 citing *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001).

Because a showing of bioequivalence is required in the context of an ANDA filing, the Federal Circuit found that that a generic manufacturer would be motivated to copy the formulation of the branded manufacturer. Although the Federal Circuit decision was non-precedential, other District Courts have cited to this decision and the rationale therein. See *Novo Nordisk A/S v. Caraco Pharm. Labs.*, 775 F. Supp.2d 985, 1017 (E.D. Mich. 2011); *Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 718 F. Supp.2d 382, 443-44 (S.D. N.Y.2010).

Levofloxacin is marketed under the tradename Levaquin® by Daiichi Pharmaceuticals and Ortho-McNeil Pharmaceuticals as an antibiotic for the treatment of a variety of bacterial infections. During ANDA litigation, a slightly different presentation of copying was presented that the District Court found persuasive, and the Federal Circuit affirmed. *Ortho-McNeil Pharmaceuticals v. Mylan*, 348 F. Supp.2d 713, 759 (N.D. W. Va., 2004) affirmed in *Ortho-McNeil Pharmaceuticals v. Mylan,* 161 Fed. Appx. 944 (Fed. Cir. 2005) under Fed. Cir. Rule 36 without opinion. Levofloxacin and ofloxacin are structurally identical, except that ofloxacin is a racemate and levofloxacin is one of the purified enantiomers. The patent covered both the racemate and the enantiomers, but Mylan chose to only copy levofloxacin (the pure enantiomer) instead of ofloxacin (the racemate). It was known that levofloxacin was therapeutically superior in many cases to ofloxacin, but Mylan argued that their decision to copy only levofloxacin was purely a business decision and not based on a comparison of the properties of the two molecules. Mylan had attempted to market their own branded antibiotic in the same class as levofloxacin and ofloxacin (i.e., quinolone antibiotics), but their compound did not receive regulatory approval due to unacceptable side effects. The court was unpersuaded and held that this was ''significant evidence of nonobviousness particularly in light of Mylan's lack of success in marketing its own'' product. *Ortho-McNeil*, 348 F. Supp.2d at 759. For a more complete description of chirality and pharmaceuticals see ''Chiral Drugs: An Overview,'' L.A. Nguyen, H. He, C. P.H., *Int. J. Biomed Sci,2(2)*, 85 (2006) which is available for free online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3614593/.

The takeaways for copying are less clear. There are conflicting court decisions in the context of ANDA litigation as to whether copying the excipients of a formulation is a secondary consideration in regard to obviousness. Despite being non-precedential, perhaps the most important decision at this time is that the Federal Circuit said copying the excipients of a branded drug in a proposed generic is not evidence of copying. The issue of copying the excipients of a branded product and the determination of bioequivalence for a generic equivalent is an open question that will undoubtedly be litigated further. This will be especially significant with an extended release formulation or when a pharmacokinetic profile is claimed to achieve optimal therapeutic efficacy or a reduction of undesirable side effects.

■ Simultaneous Invention

In all of the examples presented herein, secondary considerations, when evinced with a clear nexus to the claims, supported a conclusion of nonobviousness. When evidence of simultaneous invention is presented, there is a more nuanced analysis that may lead to the opposite conclusion. ''The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art.'' *Ecolochem v. Southern California Edison Co*., 227 F.3d 1361, 1379 (Fed. Cir. 2000) citing *The Int'l Glass Co. v. United States*, 187 Ct. Cl. 376, 408 F.2d 395, 405 (1969). Inventions independently and simultaneously made ''within a comparatively short space of time,'' are persuasive evidence that the claimed apparatus ''was the product only of ordinary mechanical or engineering skill.'' *Geo M. Martin Co. v. Alliance Machine Sys. Int'l. LLC*, 618 F.3d 1294, 1305 (Fed-.Cir.2010) citing *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925). However, ''the statute, [pre-AIA] 35 U.S.C. § 135, (establishing and governing interference practice) recognizes the possibility of near simultaneous invention by two or more equally talented inventors working independently, that occurrence may or may not be an indication of obviousness when considered in light of all the circumstances.'' *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co*., 730 F.2d 1452, 1460 (Fed. Cir. 1984).

Levoleucovorin is marketed under the tradename of Fusilev® by Spectrum Pharmaceuticals to reduce the adverse side effects of some chemotherapeutic agents. It is the purified 6S-enantiomer of leucovorin. During ANDA litigation, evidence was presented regarding simultaneous invention. *Spectrum Pharmaceuticals, Inc. v. Sandoz, Inc*., Case No. 2:12-cv-00111-GMN-NJK (D. Nevada, Feb. 25, 2015). The claims were to a pharmaceutical composition comprising at least 92 percent of one of the enantiomers of leucovorin. Studies had shown that one enantiomer (the 6S-entantiomer) was much more therapeutically effective than the other (the 6R-enantiomer), and many of the negative side effects were caused by the 6R-enantiomer. There was strong motivation in the peer-reviewed medical literature to formulate and market the 6S-enantiomer (see US 6,500,829 (the patent in the present litigation) and references cited therein). Because there was strong motivation in the prior art to create an enantiomerically pure form of leucovorin, multiple research groups worked on the problem simultaneously. Four different groups succeeded in developing a commercially viable process for the production of levoleucovorin as evinced by three different method patents. Although the District Court did not make an explicit finding that the claimed composition would have been obvious based on the secondary consideration of simultaneous invention, the clear conclusion is that the court thought the preparation of the enantiomerically pure form was well within the state of the art at the time of the invention thereby supporting the conclusion that the claims were obvious. *Spectrum Pharmaceuticals*, Case No. 2:12-cv-00111-GMN-NJK at (II)(D)((iii)(c), findings of fact ¶ 110 to ¶ 122.

Oxymorphone HCl is marketed under the tradename of Opana® by Spectrum Pharmaceuticals as an extended release formulation for the treatment of pain. It is closely related to oxycodone both structurally and in its biological activity. During ANDA litigation, a different type of simultaneous invention was argued. *Endo Pharmaceuticals, Inc. v. Amneal Pharmaceuticals*, Civil Action Nos. 14-1382-RGA, 14-1389-RGA (D. Del., Oct.

7, 2016). The claims were similar to those previously discussed for oxycodone, *supra*, in that they were directed to a pharmaceutical formulation where a similar impurity (also abbreviated ABUK) was greatly reduced. *In re Oxycontin Antitrust Litigation*, 994 F. Supp.2d at 367 affirmed in *Purdue Pharma*, 811 F.3d at 1345. The defendant argued that because the method of development for the low-ABUK oxycodone was similar to the method for the development of low-ABUK oxymorphone, simultaneous invention occurred, thereby illustrating the state of the art at the time of the invention. The court rejected this comparison and held that the because low-ABUK oxycodone is not low-ABUK oxymorphone, it was not evidence of any secondary considerations in the obviousness analysis. *Endo Pharmaceuticals*, Civil Action Nos. 14-1382-RGA, 14-1389-RGA at § I(C)(iv)¶ 2. The question of how this would have turned out with a method claim for preparing the low impurity composition remains unanswered.

During risedronate ANDA litigation, it was held that even an unpublished patent application can illustrate the state-of-the-art and simultaneous invention. *Warner Chilcott Co. v. Teva Pharmaceuticals*, 89 F. Supp.3d 641 (D. N.J. 2015). When the patent was filed, it was known that bisphosphonates (the class of drugs to which risedronate belongs) had to be taken on an empty stomach because calcium present in food bound to the drug molecule, which inhibited intestinal absorption. Patients often did not follow the administration instructions, so they received a therapeutically ineffective dose. It was also known that ethylenediamine tetraacetic acid (EDTA) was a calcium chelator that bound calcium, thereby preventing it from binding to a drug molecule. The question was whether or not it was obvious to combine risedronate and EDTA in a single formulation to overcome the food effect. Evidence was introduced at trial that Procter & Gamble used their commercial strength to pressure Takeda into withdrawing a Japanese Patent Application before publication so that it would not become prior art against their own patent application. (Note: Warner Chilcott acquired the patents at issue when they purchased Procter & Gamble's pharmaceutical division). The Takeda application addressed the exact same problem (i.e., the food effect) for the exact same class of drugs (i.e., bisphosphonates) and had an earlier priority date. Takeda agreed to withdraw their application, which allowed the Procter & Gamble patents to issue. However, Takeda introduced the unpublished patent application during litigation as evidence of simultaneous invention. The court held that a person skilled in the art would be aware of the problem with bisphosphonates, would understand that EDTA is a calcium chelator and would know how to ''conquer the bisphosphonate food effect and achieve 'pharmaceutically effective absorption.' '' *Id.* at 671. ''In light of all the circumstances, some satisfaction of a need is not sufficient to outweigh the extensive evidence in the prior art showing that coadministration of EDTA and a bisphosphonate would have the benefit of reducing the food effect and *the evidence of Takeda's simultaneous invention* of a formulation that would meet the need to a similar extent (emphasis added).'' *Id.* at 682.

The key takeaway here is that simultaneous invention can be a double-edged sword. Although the statute specifically contemplates this possibility without any negative consequences toward patentability, the courts seem to think differently. It's very possible with the America Invents Act (AIA) and the eventual winding down of interference proceedings under pre-AIA 35 U.S.C. § 135 that this will automatically become a negative factor in an obviousness analysis.

Conclusion Secondary considerations are an important factor in arguing for or against obviousness, and the courts have held that they may be the most important of the four *Graham* factors. Each factor requires a different type of evidence, and expert testimony will often be necessary to provide the necessary support. There is no specific type of evidence that will always support a conclusion of nonobviousness, and the courts have shown a willingness to closely examine the evidence to ensure a clear nexus between the claims and the marketed product exists. Some of the factors are closely related and evidence for one can support another. Not all secondary factors will support a conclusion of nonobviousness, so it is important when either prosecuting or litigating the issue of nonobviousness to ensure that the evidence supports only one possible conclusion. Valid alternative interpretations will reduce the impact of the evidence, and in some instances, may support an obviousness determination instead of nonobviousness.

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