Keywords: **Doctrine of inherency, inherency in an obviousness context.**

General: **A determination of obviousness based on the doctrine of inherency must show that the property at issue is the "natural result" flowing from the operation as taught. A "high standard" is required to invoke the doctrine of inherency in an obviousness context.**

Par Pharm, Inc. v. TWi Pharm, Inc.
(2014-1391 Fed. Cir. 2014)
December 3, 2014

I. Facts and Procedural History

Megestrol acetate (hereinafter, "megestrol") has been known to treat wasting, for example, in cancer patients, by increasing body mass and patients appetites. In 1993, Bristol-Myers Squibb began marketing an oral suspension of microsized megestrol particles under the name "Megace OS." Megace OS is specifically focused on treatments of anorexia and cachexia in AIDS patients, and proved a commercial success. Other drug manufacturers, including Par Pharmaceutical (hereinafter, "Par"), submitted an Abbreviated New Drug Application (ANDA) under the Hatch-Waxman Act to seek approval to market generic versions of Megace OS. Par's application was granted Federal Drug Administration (FDA) approval and Par began selling a generic version of Megace OS.

Par continued research on megestrol, and came up with a nanosized megestrol formulation by applying a NanoCrystal technology available from Elan Pharmaceuticals. After the nanosized megestrol was produced, Par discovered that Megace OS demonstrated a strong food effect, such that Megace OS did not work as well when patients were fasting. By way of contrast, the nanosized megestrol did not demonstrate a strong food effect. This difference in food effect is important because AIDS patients typically have substantially reduced appetites. Par applied for a U.S. patent, which was initially denied based on prior art that discussed both microsized megestrol and the NanoCrystal technology. Par amended the claims to add two "wherein" clauses that address the lack of a food effect in the nanosized megestrol, as follows:

1. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:

(a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
(b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and
(c) the administration is once daily;
wherein after a single administration in a human subject of the formulation there is no substantial difference in the Cmax of megestrol when the formulation is administered to the subject in a fed versus a fasted state, wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

The amended claim 1 was found allowable and a U.S. Patent No. 7,101,576 (hereinafter, "576") issued on September 5, 2006. Par was granted FDA approval to sell the nanosized megestrol formulation as "Megace ES." Megace ES is indicated for use "without regard to meals," unlike Megace OS, where "the effect of food on bioavailability of Megace OS has not been evaluated." Par claimed that Megace ES is a commercial success, generating $600M in sales since sales

began. TWi Pharmaceuticals, Inc. (hereinafter, "TWi") filed an ANDA seeking to market a generic formulation of Megace ES, and provided Par proper notice of the TWi ANDA application and its Paragraph IV certification that asserted that the '576 patent is invalid, or would not be infringed by TWi's nanosized megestrol formulation. Par filed suit on September 1, 2011, under 35 U.S.C. § 271(e)(2)(A).

The U.S. District Court for the District of Maryland held that the patent was invalid as obvious in view of the combination of 1) prior art analyses of the pharmacokinectic properties of megestrol (e.g., microsized megestrol), and 2) prior art detailing the use of nanoparticle technology in drug formulation (e.g.,. NanoCrystal technology). More specifically, the district court held that TWi proved that all elements of the claimed invention where disclosed in the prior art, and that a person of ordinary skill in the art would be motivated to combine microsized megestrol with NanoCrystal technology to abrogate the food effect with a reasonable expectation of success. The district court further held that while TWi was unable to prove by clear and convincing evidence that a food effect for microsized megestrol was known in the prior art, the recitation that "there is no substantial difference in the Cmax of megestrol when the formulation is administered to the subject in a fed versus a fasted state" of claim 1 is "an inherent result" of nanosized megestrol "even if it was not previously know in the prior art that a food effect existed." *Post-Trial Memorandum*, at 13-21. Par appealed the decision to the Federal Circuit.

II. Issues

A. Did the district court err in its inherency analysis?

B. Did the district court correctly decide the questions of motivation to combine the prior art and reasonable expectation of success?

III. Discussion

A. Yes. The Federal Circuit noted that a "party must … meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—*the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art*." Emphasis added. Here, while it *may* be true that reducing the formulation into the nanometer range could result in *some* improvement in the food effect, there is no evidence that the reduction of megestrol particles into the nanometer range *naturally results* in "no substantial difference" as recited in claim 1. The Federal Circuit further quoted *In re Oelrich*, 666 F.2d at 581, stating that "[i]nherency, however, may not be established by probabilities of possibilities… the mere fact that a certain thing may result from a given set of circumstances is not sufficient." The Federal Circuit noted that the district court's record was silent as to a conclusion that TWi failed to present evidence sufficient to demonstrate that the claimed food effect limitations are naturally flowing from or are present in the prior art combinations. Accordingly, the Federal Circuit deemed it proper to remand for a determination of whether or not the food effect as claimed is necessarily present in the prior art combination.

B. Yes. Par argued that a person of ordinary skill in the art would have no motivation to combine the references because the person would not have known of the food effect. However, the Federal Circuit held that the motivation to combine need not be restricted to the same motivation as the patentee (e.g., food effects), but could include alternate motivations provided by TWi, such as reducing viscosity of the microsized megestrol. As for a reasonable expectation of success, the

district court was correct in finding that the technology of nanoparticle formulation (e.g., NanoCrystal technology) was sufficiently advanced at the time of the invention such that a person of ordinary skill in the art could reasonably expect that nanoparticle megestrol could be achieved.

IV. Conclusion

When inherency is applied in the context of an obviousness rejection, a high standard is required. More specifically, the high standard requires that the limitation at issue is *necessarily present* or *the natural result* of the combination of elements explicitly disclosed in the prior art. Simply because the combination *may result* in the claimed subject matter is not sufficient to meet the high standard.