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# Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc. (Fed. Cir. December 3, 2014)

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# Background

- In 1993, Bristol-Myers Squibb began selling an oral suspension of micronized megestrol (Megace OS) for the treatment of anorexia and cachexia in AIDS patients.



# Background

- Par applied for and received approval to market a generic micronized megestrol formulation.
- Par also continued to experiment with megestrol by reducing the particle size to the nanometer range.



# Background

- Par contracted with Alkermes Pharma Ireland (also named as a Plaintiff and formerly known as Elan Pharmaceuticals) to use its “NanoCrystal” technology to create nanosized megestrol.



# Background

- Par discovered that Megace OS has a strong food effect.
  - Patients taking Megace OS with a meal showed a higher rate of absorption compared with patients taking Megace OS in a fasting state.
  - However, the nanosized megestrol showed a greatly reduced food effect.

# Background

- USPTO rejected Par's initial claims covering methods for use of nanosized megestrol formulations as obvious in light of prior art that discussed micronized megestrol formulations and Elan's NanoCrystal technology.
- Par amended the claims to recite the lack of a food effect.

# Background

- USPTO found the amended claims to be allowable and the application issued as U.S. Patent No. 7,101,576.

(12) **United States Patent**  
**Hovey et al.**

(10) **Patent No.:**      **US 7,101,576 B2**  
(45) **Date of Patent:**      **Sep. 5, 2006**

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# Claim 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...



## Claim 1 (cont.)

...wherein after a single administration in a human subject of the formulation there is no substantial difference in the C<sub>max</sub> 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.

# Background

- The FDA approved Par's New Drug Application for Megace ES, which was indicated for use “without regard to meals.”
- In contrast, Megace OS stated that the effect of food on bioavailability has not been evaluated.



# Background

- TWi filed an ANDA seeking approval to market a generic form of nanosized megestrol.
- In response, Par filed suit for infringement in the U.S. District Court for Maryland.
- TWi responded, among other things, that the claims are invalid as obvious under 35 U.S.C. 103.



# TWi's Obviousness Argument

- TWi bases its obviousness argument on multiple pieces of prior art.
- The prior art, including the label for Megace OS, demonstrated that micronized oral suspensions of megestrol were used in the treatment of anorexia, cachexia, and unexplained weight loss for AIDS patients.

# TWi's Obviousness Argument

- Several pieces of prior art disclosed the use of nanoparticle technology in drug formulation.
  - US 5,399,363 discussed the use of NanoCrystal technology and listed megestrol as one of many preferred anticancer agents for use with the NanoCrystal technology.
  - Other prior art noted the increased bioavailability and decreased food effect that results from nanosizing drug particles.

# District Court

- After a five day bench trial, the district court concluded that the '576 patent was invalid as obvious.
  - Although TWi showed megestrol acetate was a known drug with poor bioavailability, TWi failed to prove that Megace OS had a known bioavailability problem or a known food effect.
  - Regardless, TWi proved that all elements of the claimed invention were disclosed in the prior art.

# District Court

- Even though the prior art did not explicitly disclose the food effect differences as claimed, the district court concluded that the claimed food effect is an inherent property of the obvious nanoparticulate formulation.

# Issue

- Both Par and TWi agree that essentially all of the substantive limitations in the independent claims are present in the prior art.
- The issue is whether the food effect limitations are disclosed in the prior art.
- Both TWi and the district court assert that these limitations are an inherent property of the formulation disclosed by the obvious combination of prior art elements.



# Federal Circuit

- Before O'Malley, Wallach, and Hughes.
- Opinion by O'Malley.

# Federal Circuit

- The Federal Circuit agreed that there was no known food effect for megestrol in the prior art.
- However, the Federal Circuit concluded that the district court erred in its inherency analysis.

# Case Law Relied Upon by Federal Circuit

- Inherency may not be established by probabilities or possibilities (*In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)).
- “That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.” *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).
- Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established (MPEP 2141.02(V)).

# Case Law Relied Upon by Federal Circuit

- *Hansgirk v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939):
  - The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

# Federal Circuit Conclusion

- The concept of inherency must be limited when applied to obviousness and is present only when the limitation at issue is the “natural result” of the combination of prior art elements.

# Federal Circuit Conclusion

- A party must, therefore, 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.

# Federal Circuit's Reasoning

- The Federal Circuit determined that the district court did not require that TWi present evidence sufficient to prove inherency under this standard.
- TWi's expert testified that an improvement in bioavailability necessarily results in a decrease in any food effect, and TWi presented evidence that a reduction in particle size improves bioavailability.
- Therefore, the district court concluded that the reduced particle size would lead to a reduced food effect.

# Federal Circuit's Reasoning

- However, the Federal Circuit stated that the district court's analysis ignores the claim limitations at issue. Claim 1 requires “no substantial difference in  $C_{max}$ ” between the fed and fasted states.



# Federal Circuit's Reasoning

- The district court's broad conclusions regarding the effect of particle size on bioavailability and food effect are not commensurate with the actual limitations at issue.
- While it *may* be true that a reduction in particle size naturally results in *some* improvement in the food effect, the district court failed to conclude that the reduction in particle size naturally results in “no substantial difference” in food effect.

# Federal Circuit

- Although the district court applied the incorrect standard for inherency in its obviousness analysis, the Federal Circuit could not conclude that TWi failed to present evidence sufficient to demonstrate that the *claimed* food effect limitations necessarily are present in the prior art combinations.
- The Federal Circuit vacates the district court's inherency analysis and remands to determine if TWi presented clear and convincing evidence that demonstrates that the food effect *as claimed is necessarily present* in the prior art combination.

# Other Issues

- Did the district court err in finding a motivation to combine megestrol with nanoparticle technology due to the known viscosity and interpatient variability problems with micronized megestrol?
- No, there is no question that the NanoCrystal technology presented a suitable option for reducing interpatient variability and viscosity in megestrol formulations.

# Other Issues

- Did the district court err in finding that TWi proved a reasonable likelihood of success in combining megestrol with nanoparticle technology?
- No, Elan's marketing materials made clear that the use of nanoparticle technology in formulation chemistry had become fairly reliable and showed consistent results regarding bioavailability, viscosity, and interpatient variability.

# Other Issues

- Did the district court err in concluding that a prior art reference (Graham) did not teach away from combining megestrol with the NanoCrystal technology?
- No, Graham merely cautioned a person skilled in the art that rapid absorption with rapid elimination and low blood plasma concentration may cause Megace OS to be ineffective.

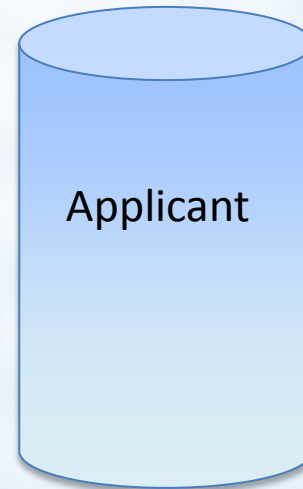
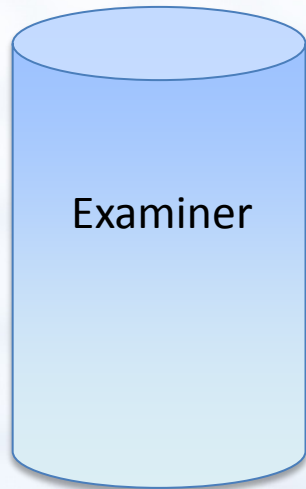
# Holding

- Although the Federal Circuit agreed with the district court's analysis and conclusions on motivation to combine and reasonable expectation of success, the Federal Circuit vacated the district court's judgment that the '576 patent is obvious and remanded for further analysis of the food effect limitation consistent with the precedent on inherency.

# Practice Points

- This case provides an important clarification on the issues of inherency as it relates to obviousness over a combination of references. Specifically, USPTO examiners will often assert that certain claimed properties are inherent to a prior art combination. The *Par* case serves as a reminder that the results achieved from combining the references had to be expected at the time of invention for obviousness to be established.

# Analogy





# Practice Points

- Functional claim language should be given full weight.

# Analogy

- A method for increasing fun, comprising:
  - providing people in a room; and
  - playing upbeat music;
  - wherein spontaneous dancing occurs to obtain increased fun.

<http://youtu.be/jeMdBssuCAw>

Questions?  
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