METHODS OF TREATMENT SURVIVE ANOTHER § 101 CHALLENGE – *PERNIX IRELAND PAIN DAC V. ALVOGEN MALTA OPERATIONS LTD.*

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On May 15, in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*,[1] the U.S. District Court for the District of Delaware upheld two sets of method of treatment patents as claiming patent eligible subject matter under 35 U.S.C. § 101 ("§ 101"). The court described the patents as being "directed to methods of treating pain in patients with hepatic impairment, i.e. comprised liver function," and as the patents claim formulations with similar release profiles for patients with and without hepatic impairment, the claims involved natural phenomena inherent in human biology. The court distinguished *Mayo*[2] and relied upon two recent Federal Circuit cases to uphold the method of treatment claims as patent eligible.

BACKGROUND

The case arose out of Alvogen Malta Operations Ltd.'s ("Alvogen") filing an Abbreviated New Drug Application with a paragraph IV certification seeking approval to market a generic version of Pernix Ireland Pain DAC and Pernix Therapeutics LLC (collectively "Pernix")'s Zohydro® ER (hydrocodone bitartrate extended-release capsules) before the expiration of Pernix's U.S. Patent No. 9,265,760 ("the '760 patent") and U.S. Patent No. 9,339,499 ("the '499 patent") (together, "the asserted patents"). Pernix sued Alvogen for infringement, asserting nine claims of the asserted patents. The claims in the asserted patents encompass formulations of extended release hydrocodone that have release profiles that are similar for both healthy and hepatically-impaired patients. As a result, the starting dose does not need to be adjusted for patients with hepatic impairment.

All nine asserted claims recite a "method of treating pain in a patient having mild or moderate hepatic impairment," and all include the phrase "administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate."

The patents explain that the "oral dosage units are preferably comprised of an immediate release component and a sustained release component. Preferably the sustained release component comprises a controlled release polymer . . . such that the release profile . . . is largely pH independent."[3] The patents state that preferably hydrocodone is the only opioid analgesic that is present, specifically excluding acetaminophen.[4] The patents direct that preferably 80% of the hydrocodone resides in the immediate release component of the drug,[5] as the

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extended release of the drug has been shown to have different reaction profiles in patients with hepatic impairment.[6]

The court characterized the asserted claims as falling into three categories:

> First, in addition to the "administering" step, claim 1 of the '760 patent includes the limitation "wherein the starting dose is not adjusted relative to a patient without hepatic impairment." Second, claims 2–4 and 11 of the '760 patent all depend on claim 1, and each of those dependent claims recites different components of the release profile, i.e., the way a patient's body breaks down the drug, as measured by the maximum concentration of drug in the patient's blood (C_{max}) and the measure of total exposure of the drug over time (AUC0–inf.). Specifically, each claim adds that the dosage unit does not result in increasing the maximum or total exposure of hydrocodone in subjects with mild or moderate hepatic impairment by more than a certain amount relative to subjects not suffering from mild or moderate hepatic impairment. Finally, claims 12, 17, and 19 of the '760 patent, and claim 1 of the '499 patent, are likewise directed to methods of treating pain in a patient having mild or moderate hepatic impairment. Each of those claims includes limitations regarding the release profile of the dosing unit, but that group of claims does not include or incorporate a limitation that the starting dose is not adjusted relative to a patient without hepatic impairment.[7]

SUBJECT MATTER ELIGIBILITY

Alvogen asserted that the claims of the '760 patent and the '499 patent are directed toward ineligible patent subject matter. Specifically, Alvogen argued that the patent claims are not eligible subject matter because the claims are "premised on the relationship between [hepatic impairment] and the bioavailability of hydrocodone in the body after administration of Devane's [extended release hydrocodone] prior art formulation—namely that the response of the human body to this formulation is similar in patients with and without mild or moderate [hepatic impairment]."

The court set out the two-step process for evaluating patent eligibility under § 101. First, "determine whether the claims at issue are directed to a patent-ineligible subject matter" such as a natural law.[8] If the answer to the first question is yes, then determine whether the elements of each claim, both individually and in an ordered combination, "transform the nature of the claim into a patent-eligible application."[9]

The court found that the "the asserted claims are not directed toward a patent-ineligible concept[.]"[10] The court stated that the asserted claims in this case are distinguishable from *Mayo* because the representative claim in *Mayo* recited a two-step method that involved administering a known drug and using routine processes to determine the level of a certain metabolite.[11] The claim in *Mayo* also included a wherein clause which "'at most added[ed] a suggestion that [doctor] should take those [natural] laws into account when treating his patient . . .

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while trusting [the doctor] to use those laws appropriately where they are relevant to their decision making.'"[12] Thus, the claims in *Mayo* "'added nothing of significance to the natural laws themselves.'"[13] In contrast, the court here found that the asserted claims "do more than merely report . . . physiological responses."[14] They describe an application of the relationship between a specific dosage regimen to treat a specific condition based on the patient's medical status.[15] For instance, the '760 patent teaches using an extended release formulation of hydrocodone bitartrate wherein the starting dose is "not adjusted relative to a patient without hepatic impairment" and both the '760 patent and the '499 patent claim using a "specific extended release formulation of hydrocodone bitartrate that has a particular release profile."[16]

According to the court, two recent decisions at the U.S. Courts of Appeals for the Federal Circuit were instructive in reaching the conclusion that the claims included something more than the natural law itself. First, the court looked to *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, which the court here cited for the principle that patents which "recite processes to achieve a desired outcome, e.g., methods of treating disease" are generally not patent-ineligible.[17] The court continued its analysis by looking to the Federal Circuit's most recent case on methods of treatment. In *Vanda Pharmaceuticals, Inc. v. West-Ward Pharmaceuticals International Ltd.*, the Federal Circuit held that "a method of treatment claim that adjusted dosage based on whether the patient had normal or lower enzyme activity was patent-eligible under section 101."[18]

The court concluded that the asserted claims required more than an application of a natural law, and it determined that they were directed to patent-eligible subject matter under § 101.

CONCLUSION

Despite the differences in the three groups of challenged claims, the court treated all three groups in the same way for the purposes of the patent eligibility analysis. For example, the court did not give additional weight to the added details regarding the components of the release profile in the second set of claims.

Additionally, the treatment step in the asserted claims contained a negative limitation: the starting dose was *not* adjusted relative to a patient without hepatic impairment. The court, however, treated the limitation in the same way that the Federal Circuit treated the active dosing step in the *Vanda* claims—as an *application* of an observed natural relationship.

Accordingly, when drafting patent applications, it may be helpful to consider whether claims directed to both active steps or negative limitations better convey a transformative application of a natural relationship, and not the mere observation of that relationship.

Notes

[1] 1:16CV00139, 2018 WL 2225113 (D. Del. May 15. 2018).
[2] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 78-79 (2012).
[3] U.S. Patent No. 9,265,760 col. 4, l. 66–col. 5, l. 5.

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[4] *Id.* at col. 5, l. 8.
[5] *Id.* at col. 5, l. 13.
[6] *Id.* at col. 2, l. 41–col. 4, l. 36.
[7] Pernix, 2018 WL 2225113 at 2.
[8] Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014).
[9] *Id.* quoting Mayo 566 U.S. at 66, 78-79.
[10] Pernix, 2018 WL 2225113 at 24.
[11] *Id.* at 22.
[12] *Id.* quoting Mayo, 566 U.S. at 74–75.
[13] *Id.* quoting Mayo, 566 U.S. at 87.
[14] *Id.* at 23.
[15] *Id.*
[16] *Id.*
[17] *Id.* quoting Litigation Management Ltd. v. CellzDirect, Inc., 827 F.3d 1042 (Fed. Cir. 2016).
[18] *Id.* citing Vanda Pharmaceuticals, Inc. v. West-Ward, 887 F.3d at 1121.

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