**Keywords:** **adequate written description, negative limitation, loading dose**

**General:** **A lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support, however, the written description may take any form and the test for written enablemen for a negative claim includes an examination of how a person of skill in the art would read the disclosure—not the exact words used in the specification.**

***Novartis Pharms. Corp. v. Accord Healthcare, Inc.***
United States Court of Appeals, Federal Circuit
No. 2021-1070
Decided January 3, 2021

## I. Facts

Novartis Pharmaceuticals Corp. ("Novartis") owns U.S. Patent No. 9,187,405 ("the '405 patent"), which is directed towards uses of an S1P receptor modulator (a chemical compound) for the treatment or prevention of RRMS disease. The '405 patent claims methods to treat RRMS disease with fingolimod (also known as 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in the '405 patent) or a fingolimod salt, such as fingolimod hydrochloride, at a daily dosage of 0.5 mg *without an immediately preceding loading dose*. Novartis markets a 0.5 mg daily dose of fingolimod hydrochloride under the brand name Gilenya.

HEC Pharm Co., Ltd. and HEC Pharm USA Inc. (collectively, "HEC", which is the only remaining defendant at trial from more than two dozen generic drug makers sued by Novartis under 35 U.S.C. § 271(e)(2)) filed an Abbreviated New Drug Application ("ANDA") seeking approval to market a generic version of Gilenya. Novartis sued, alleging that HEC's ANDA infringes all claims of the '405 patent. Representative claim 1 of the '405 patent recites:

> 1. A method for reducing or preventing or alleviating relapses in Relapsing-Remitting multiple sclerosis in a subject in need thereof, comprising orally administering to said subject 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol, in free form or in a pharmaceutically acceptable salt form, at a daily dosage of 0.5 mg, *absent an immediately preceding loading dose regimen*. (Emphasis added.)

Defendant HEC maintained that the '405 patent was invalid because its specification and its priority British patent application (GB0012721) filed in 2006 did not provide an adequate written description of an invention comprising the "*absent an immediately preceding loading dose regimen*" limitation under 35 U.S.C. § 112(a). After a four-day bench trial, the district court found

that HEC's ANDA product would infringe claims 1-6 of the '405 patent. The court also found that HEC had not shown that the '405 patent is invalid for insufficient written description for the claimed 0.5 mg daily dose limitation and for the no-loading-dose limitation. HEC appealed to Federal Circuit by challenging the district court's decisions concerning the '405 patent's written description of the two limitations: the dosage limitation and the negative limitation.

## II. Issue

Did the district court err in finding that HEC failed to show that the '405 patent assigned to Novartis is invalid because of insufficient written description for (1) the dosage limitation, and for (2) the negative limitation?

## III. Discussion

(1) No. Regarding written description for the dosage limitation, the Federal Circuit found no clear error in the district court's holding that the 0.5 mg/day dosage limitation is adequately described. The district court's holding is supported by the specification and ample expert testimony interpreting that specification.

During the appeal, HEC argued that, as of the 2006 priority date, the inventors did not possess a 0.5 mg daily dose of fingolimod and the 0.5 mg/day was considered too low to be effective to treat RRMS. HEC described Novartis's calculation of the 0.5 mg/day human dose as derived from the lowest disclosed dose in the rat EAE model and as "undisclosed mathematical sleights of hand." HEC also argued that the Prophetic Trial, which listed a 0.5 mg daily dose along with two other dosages, did not provide sufficient written description of the 0.5 mg dose. Finally, HEC asserted that "blaze marks" directing a skilled artisan to the 0.5 mg daily dose were absent from the '405 patent. The Federal Circuit found HEC's arguments were not convincing.

The Federal Circuit stated that the Prophetic Trial and the EAE model provided sufficient written description to show that, as of the priority date, the inventors possessed a 0.5 daily fingolimod dosage as claimed in the '405 patent. The Prophetic Trial describes dosing RRMS patients with fingolimod hydrochloride at daily dosages of 0.5, 1.25, or 2.5 mg. *See* '405 patent col. 11 ll. 8-16. The Prophetic Trial's disclosure of two other dosages does not detract from the written description of the claimed dose. Nor do disclosures of dosage ranges in other areas of the specification lead away from the claimed dose.

Regarding HEC's attack on the expert testimony underlying the district court's determination that the EAE experiment described a 0.5 mg daily human dose, the Federal Circuit disagreed as a "disclosure need not recite the claimed invention *in haec verba*." *Ariad, 598 F.3d at 1352*. The disclosure need only "clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Id. at 1351*. To accept HEC's argument would require the court to ignore the perspective of the person of ordinary skill in the art and require literal description of every limitation, in violation of the precedent. As such, the Federal Circuit found no clear error in the district court's reliance on expert testimony in finding description of the 0.5 mg daily human dose in the EAE experiment results.

The Federal Circuit rejected HEC's argument that the '405 patent did not have necessary "blaze marks" pointing to the 0.5 mg daily dose. "Blaze marks" direct an investigator of ordinary

skill in the art to the claimed species from among a forest of disclosed options are not necessary in this case. In cases where the specification describes a broad genus and the claims are directed to a single species or a narrow subgenus, the Federal Circuit have held that the specification must contain blaze marks "that would lead an ordinarily skilled investigator toward such a species among a slew of competing possibilities." *Novozymes v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1349 (Fed. Cir. 2013).* "Blaze marks" are not necessary where the claimed species is expressly described in the specification, as the 0.5 mg daily dosage is here. *See, e.g., Snitzer v. Etzel, 465 F.2d 899, 902, 59 C.C.P.A. 1242 (C.C.P.A. 1972).*

The Federal Circuit stated that much of HEC's argument is directed to its assertion that no one, including the inventors, knew that a 0.5 mg/day dose would be effective as of the 2006 priority date. That argument fails for two reasons. First, efficacy is not a requirement of the claims. The claims require only administration of a 0.5 mg/day dose for, *inter alia*, treatment purposes. The district court found that the purpose limitations are adequately described, and HEC has not appealed that finding. Second, as explained above, the EAE model provides evidence that the inventors knew that a 60% lower dose would be effective.

(2) No. Regarding written description for the negative limitation, the Federal Circuit found no clear error in the district court's holding that a skilled artisan would read the '405 patent's disclosure to describe the "absent an immediately preceding loading dose" negative limitation.

During the appeal, HEC argued that there was no written description of the negative limitation because the '405 specification contains no recitation of a loading dose "or its potential benefits or disadvantages at all." HEC further argued that the district court's finding of written description of the negative limitation within the '405 specification contradicted the district court's finding that Kappos 2006, which is similarly silent as to loading doses, does not anticipate the claims. The Federal Circuit found both arguments unavailing.

The Federal Circuit stated that it is well established that there is no "new and heightened standard for negative claim limitations." *Inphi Corp. v. Netlist, Inc., 805 F.3d 1350, 1356 (Fed. Cir. 2015).* The Federal Circuit is aware of no case that suggests otherwise. While HEC asserted that "[i]t is well-settled law that silence alone cannot serve as a basis for" a negative limitation, HEC identified no case that actually supports that proposition. To the contrary, the Federal Circuit repeatedly have resisted imposition of heightened written description standards for negative limitations, such as that urged by HEC. In asserting that "silence alone cannot serve as a basis for" a negative limitation, HEC attempted to create a new heightened written description standard for negative limitations. In doing so, HEC ignored a central tenet of written description jurisprudence—that the disclosure must be read from the perspective of a person of skill in the art—as well as precedent stating that the disclosure need not describe a limitation *in haec verba*. *See*, e.g., *All Dental Prodx, LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779 (Fed. Cir. 2002).* Additionally, the Federal Circuit noted that while M.P.E.P. § 2173.05(i) states "[t]he mere absence of a positive recitation" is not enough and "silence alone is insufficient," it is how a skilled artisan reads a disclosure that matters, not the exact words used; the written description may take any form, so long as a skilled artisan would read the disclosure as describing the claimed invention.

The Federal Circuit found that in determining that there is adequate written description of the negative limitation, the district court correctly, and quite carefully, conducted "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" as required by precedent. *See Ariad, 598 F.3d at 1351*. The district court credited testimony from Novartis' experts, as well as the testimony from HEC's own expert witness, Dr. Hoffman, who agreed that "a loading dose is a higher-than-therapeutic level dose, usually given…as the first dose." Based on these testimonies, the district court concluded that the "absence of an immediately preceding loading dose from the specification, and from the Prophetic Trial, would tell a person of skill that loading doses are excluded from the invention." The Federal Circuit reviewed the evidence cited by the district court and discerned no clear error in the court's analysis or conclusions.

## IV. Conclusion

The Federal Circuit affirmed the district court's decision. In addition, the Federal Circuit pointed out that case law makes clear that "[c]compliance with the written description requirement is essentially a fact-based inquiry that will ''necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 963 (Fed. Cir. 2002)*. Additionally, while the M.P.E.P. states: "the mere absence of a positive recitation is not a basis for an exclusion" and "a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support," the M.P.E.P. also states that the written description may take any form and the holding reiterates that what is critical is how a person of skill in the art would read the disclosure—not the exact words used in the specification.