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Locke Lord QuickStudy: Functional Antibody Claims: Setting the Bar for Enablement

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On February 11, 2021, in a unanimous decision, the Federal Circuit affirmed the district court's holding that Amgen Inc., Amgen Manufacturing, Ltd., and Amgen USA, Inc.'s (collectively, "Amgen's") antibody composition claims are invalid for lack of enablement. *Amgen Inc. v. Sanofi, Aventisub LLC*, No. 20-1074 (Fed. Cir. 2021).

The patented technology relates to an antibody composition for treating high levels of cholesterol in the blood or hypercholesterolemia. *See id*. at 3. A high level of low-density lipoprotein ("LDL") cholesterol, often called "bad" cholesterol, is associated with heart disease. *Id.* LDL receptors ("LDLRs"), present on the surface of cells, bind to LDL cholesterol in the blood and regulate the amount of circulating LDL cholesterol. *Id.* The enzyme, proprotein convertase subtilisin/kexin type 9 ("PCSK9"), in turn binds and degrades LDLRs removing them from the cell's surface. *Id.* Specific antibodies may bind and block PCSK9, preventing the degradation of LDLRs and allowing them to continue regulating the levels of circulating LDL cholesterol. *Id.*

Two patents owned by Amgen, U.S. Patent Nos. 8,829,165 ("the '165 patent") and 8,859,741 ("the '741 patent"), generally describe antibodies that bind to one or more of fifteen amino acid residues in PCSK9 and block PCSK9 from binding to LDLRs. *Id.* at 4. The patent specifications disclose amino acid sequences for twenty-six antibodies, including the antibody designated as "21B12." *Id.* at 3-4. 21B12 is present in the monoclonal antibody medication marketed by Amgen as Repatha® having the generic name evolocumab. *See id.* at 4. In the claims at issue, the antibodies are defined by their dual-function: binding to combinations of amino acid residues in PCSK9 (ranging from one to all residues); and blocking the PCSK9/LDLR interaction. *Id.* at 5.

This is the second time the parties have been before the Federal Circuit appealing decisions on the '165 and '741 patents. *Id.* at 5. Amgen initially filed suit against Sanofi, Aventisub LLC, Regeneron Pharmaceuticals Inc., and Sanofi-Aventis U.S. LLC (collectively, "Sanofi") on October 17, 2014 in the United States District Court for the District of Delaware, alleging infringement of a number of U.S. patents, including the '165 and '741 patents. *Id.* Sanofi stipulated to infringement of specific claims and the parties proceeded to a jury trial on issues of validity in March 2016. *Id.* The district court granted JMOL of nonobviousness and no willful infringement during trial. *Id.* At the close of trial, the jury determined that the patents were not invalid on the grounds of lack of enablement and written description. Sanofi appealed to the Federal Circuit. *Id.*

The Federal Circuit held that the district court erred in its evidentiary rulings and jury instructions regarding Sanofi's defenses that the patents lack written description and enablement and remanded for a new trial. *Id.* at 5-6. On remand, the jury again found that Sanofi failed to prove that the asserted claims were invalid for lack of written description and enablement. *Id.* at 6. Sanofi, however, moved for JMOL and the district court granted the

motion. Amgen then appealed to the Federal Circuit. *Id.*

An exemplary claim that was found to be invalid for lack of enablement by the district court ?and addressed by the Federal Circuit is claim 19 of the '165 patent. *Id.* at 4. Both claim 19 and claim 1, on which it depends, are listed below:

1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.

Id.

Amgen argued that a proper analysis of the *Wands* factors would show that the claims at issue are enabled because there would be no undue experimentation to obtain antibodies fully within the scope of the claims. *Id.* at 8. Sanofi contended that undue experimentation would be involved as millions of antibody candidates fell within the scope of the claims, there was insufficient guidance in the disclosures, antibody generation is unpredictable, and substantial trial and error would be involved in practicing the full scope of the claims. *Id.*

The Federal Circuit considered the *Wands* case itself and precedent set in the *Enzo*, *Wyeth*, and *Idenix* cases. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, 928 F.3d 1340 (Fed. Cir. 2019); *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013); *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.* 2018 WL 922125 (D. Del. Feb. 16, 2018).

The Federal Circuit found that "the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short….[I]t is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." *Id.* at 10. The Federal Circuit reasoned that "while functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 11.

The Federal Circuit agreed with the district court that the scope of the claims at issue was broad not just with the number of embodiments but that "the claims were far broader in functional diversity than the disclosed examples." *Id.* at 12. The Federal Circuit also agreed with the district court that the relevant field of science was unpredictable with respect to satisfying the full scope of the functional limitations since there was evidence only that a small subset of examples of antibodies could predictably be generated. *Id*.

The Federal Circuit concluded "[t]he functional limitations here are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude under these facts that anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments." Hence, the Federal Circuit affirmed the

district court's holding that the claims were not enabled. *Id.* at 13-14.

In practice, patentees should focus on claiming antibodies without resorting to functionality, or if functional claiming is desired, either limiting the breadth of the functionality or providing sufficient examples to support the breadth of the claims. Challengers to patents with functionally claimed antibodies should investigate whether the functionality is overly broad. Future decisions may further explore whether functional claiming in contexts other than antibodies meet the enablement requirement.

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