

# Locke Lord QuickStudy: Bayer v. Baxalta: Meeting the Large Molecule Enablement Bar

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*Bayer v. Baxalta* is a patent case dealing with several issues of claim scope, infringement, validity, and damages. *Bayer Healthcare LLC v. Baxalta Inc.*, No. 2019-2418 (Fed. Cir. Mar. 1, 2021). Here, as a follow up to our [last QuickStudy](#) regarding functional claiming of antibodies, we focus on the issue of whether the asserted claims are invalid for lack of enablement.

On March 1, 2021, the Federal Circuit affirmed the district court's decision denying Baxalta Inc. and Baxalta US Inc.'s (collectively, "Baxalta's") motion for judgement as a matter of law ("JMOL") that Bayer HealthCare LLC's ("Bayer's") polypeptide conjugate claims are not enabled. (*Id.* at 2.) The Federal Circuit found that substantial evidence supported the jury's verdict that "Baxalta failed to prove by clear and convincing evidence that the asserted claims are invalid for lack of enablement." (*Id.* at 22.)

Bayer's patented technology relates to recombinant forms of human factor VIII ("FVIII"). (*Id.* at 2.) FVIII is an essential blood-clotting protein produced by the liver. (See *id.*) FVIII is a 2,332 amino acid protein having six different structural domains: A1-A2-B-A3-C1-C2. (*Id.*) FVIII is used to treat Hemophilia A, a common hereditary blood coagulation disorder that results from defects in the gene that encodes natural FVIII. (*Id.* at 2-3.) FVIII has a short half-life and its use as a therapeutic requires frequent administration, which in turn is a barrier for patient compliance. (*Id.* at 3.) Hence, an FVIII product with a longer half-life would be beneficial for patients, as it would require less frequent administration and fewer doses might also reduce the cost of treatment. (*Id.*)

Bayer's U.S. Patent No. 9,364,520 ("the '520 patent") describes recombinant forms of FVIII that are specifically modified through PEGylation. (*Id.*) PEGylation is the process of attaching a polymer called polyethylene glycol ("PEG") to a protein. (*Id.*) PEGylation has been shown to increase a protein's *in vivo* half-life. (*Id.*) While random PEGylation of FVIII was known in the art to increase the half-life of FVIII, it had some issues. (*Id.*) Due to the hundreds of possible PEGylation sites in FVIII, there were drawbacks to random PEGylation including reduced activity, lower yield, and a heterogeneous product that made commercialization more difficult. (*Id.* at 3-4.) The '520 patent purports to overcome these drawbacks through non-random, site-directed PEGylation at the B-domain of FVIII. (*Id.* at 4.)

Bayer sued Baxalta and Nektar Therapeutics, Baxalta's collaborator, alleging that Baxalta's biologic product Adynovate<sup>®</sup>, infringed certain claims of the '520 patent. (*Id.* at 5.) Adynovate<sup>®</sup>, an extended half-life, recombinant, PEGylated FVIII replacement treatment, is made by PEGylating amino acids in FVIII that have amine groups, including the amino acid lysine. (*Id.*)

Claim 1, the only asserted independent claim of the '520 patent, recites:

1. An isolated polypeptide conjugate comprising a functional factor VIII polypeptide and one or more biocompatible polymers, wherein the functional factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or an allelic variant thereof and has a B-domain, and further wherein the biocompatible polymer comprises polyalkylene oxide and is covalently attached to the functional factor VIII polypeptide at the B-domain.??

*(Id.)*

Baxalta argued that no reasonable jury could find that the '520 patent enables the full scope of the claims because it does not enable non-random lysine PEGylation. *(Id. at 22.)* The '520 patent discloses detailed instructions about practicing the claimed invention using cysteine PEGylation and includes a working example of non-random cysteine PEGylation at the B-domain of FVIII. *(Id. at 23.)* Baxalta's expert testified that "ordinarily skilled artisans would not have known from reading the specification how to nonrandomly PEGylate FVIII with any amino acid other than cysteine." *(Id. at 24.)* The Federal Circuit, however, disagreed finding that "Bayer presented evidence to the jury bridging the gap between the patent's disclosures about cysteine PEGylation on the one hand and non-random PEGylation, including non-random lysine PEGylation, on the other." *(Id. at 23.)* The Federal Circuit relied on evidence from an inventor who testified that he did not believe that cysteine conjugation was the only way to achieve the claimed B-domain PEGylation of FVIII and multiple witnesses testifying that random lysine PEGylation was old technology known in the art and that protein chemistry was a well-defined field going back 150 years. *(Id. at 23-24.)* The Federal Circuit also relied on the testimony of Bayer's expert, who Baxalta chose not to cross-examine, that "advanced knowledge concerning amino acids—along with the fact that only a certain subset could be used for PEGylation—would have aided skilled artisans in applying the teachings in the patent to prepare a non-random lysine PEGylated conjugate without undue experimentation." *(Id. at 24-25.)*

Based on such evidence the Federal Circuit found that "Bayer presented substantial evidence from which a reasonable juror could find that the specification's disclosure of instructions as to the reaction conditions required to practice the claimed invention using cysteine PEGylation are sufficient to enable not only nonrandom cysteine PEGylation at the B-domain, but also non-random lysine PEGylation at the B-domain.?" *(Id. at 25.)*

The Federal Circuit also disagreed with Baxalta's contention that the district court legally erred by substituting the knowledge of a person of ordinary skill for the specification's lack of enabling disclosure given the absence of working examples of lysine PEGylation in the specification. *(Id.)* The Federal Circuit instead stated that it has repeatedly made clear that "the specification need not include a working example of every possible embodiment to enable the full scope of the claims." *(Id.)* Baxalta also contended that the district court legally erred by relying on testimony by Bayer's experts concerning post-priority lysine PEGylation used in Baxalta's manufacture of Adynovate<sup>®</sup>. *(Id. at 26.)* The Federal Circuit agreed that "post-priority knowledge about the 'reaction conditions' for the accused product cannot support the jury verdict of enablement." *(Id.)* However, the Federal Circuit found that any such error in this case was harmless as the district court also relied on other evidence including expert testimony "regarding the depth of knowledge in the art about protein chemistry and PEGylation at the time of the invention" and "the knowledge regarding reaction conditions and process steps, among other factors, that determine whether PEGylation is random or non-random." *(Id.)*

The Federal Circuit concluded that the district court did not err in its legal analysis and that a reasonable jury could have found the claims enabled. (*Id.* at 26-27) Hence, the Federal Circuit found that the district court correctly denied Baxalta's motion for JMOL of invalidity for lack of enablement. (*Id.* at 27.)

Thus, in contrast to the functional claiming of an antibody that the Federal Circuit recently found not enabled in *Amgen Inc. v. Sanofi Aventisub LLC*, the Federal Circuit found claims to a modified 2,332 amino acid protein enabled to the full scope where instead of using functional language, the claim identified one of six specific domains in the protein for the modification (in this case PEGylation) to occur. Despite only exemplifying cysteine PEGylation in one protein domain, the Federal Circuit found that Bayer had presented sufficient evidence for a jury to find that a person of ordinary skill in the art would have understood how to also non-randomly PEGylate other amino acids in that protein domain from the provided disclosure.

In practice, patentees should ideally ensure that sufficient disclosure supports the full scope of the claims. However, if such disclosure is limited, evidence that the field of the invention is well established and that the knowledge of a person of ordinary skill in the art is advanced can also support enablement. Challengers of these patents should take efforts to rebut this evidence based on the breadth of what is claimed versus what is disclosed in the patent, and the level of knowledge of the person of ordinary skill in the art. Given the diversity and complexity of biologic drugs, enablement will remain an evolving issue for courts to address.

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