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Protecting Antibody Innovations: Searching for Equivalents under The Doctrine of Equivalents —A Discussion of Teva v. Eli Lilly and beyond

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United States courts have recently tightened the written description requirements for antibody claims. The scope of issued claims is now often limited to antibodies with specific sequences of the CDR and the heavy chain and light chain variable domains. Patentees are concerned that competitors can easily design around patent claims by making minimum changes to the specifically claimed structural elements. Since such a design-around will not be liable for literal infringement of the claims, the question is whether a patentee can be found liable for infringement under the Doctrine of Equivalents ("DOE").

DOE applies when the accused product or process contains elements identical or equivalent to each claimed element of the patented invention.[1] Although the U.S. Supreme Court established the tests of DOE more than five decades ago[2] —the function-way-results ("FWR") test and the insubstantial differences test, case law addressing DOE issues related to biologics, especially antibodies, are scarce. This article discusses antibody case law, where in each case, the patentee failed to convince the court to find that the accused infringed the patentee's claims under DOE.

I. Courts favor the insubstantial differences test over the FWR test when assessing equivalents in antibody cases

The FWR and the insubstantial differences tests have been applied in DOE cases. However, in *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, the U.S. Supreme Court stated that while the FWR test might be suitable for analyzing mechanical devices, it often provides a poor framework for analyzing other products or processes.

Recently, in T*eva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, the court revisited these tests to determine whether a disease treatment method using an antibody having different sequences from the claimed antibody nonetheless infringes the claim under DOE.[3] More specifically, the court held that the FWR test is less appropriate for evaluating equivalents in chemical compounds because it can fail to capture substantial differences between the claim and the accused compound.[4] The court then decided the DOE issue based on the insubstantial differences test.[5]

In *Teva v. Eli Lilly*, the disputed claims are claims 18 and 21 of Teva's United States Patent No. 8,586,045 (granted on November 19, 2013).[6] Both claims depend on claim 17, and both are directed to the methods of reducing the incidence of or treating headaches with an anti-CGRP antagonist antibody.[7] Claim 18

defines the six CDR sequences, and claim 21 defines the heavy chain and light chain variable domain sequences:

> 17. A method for reducing incidence of or treating headache in a human, comprising administering to the human an effective amount of anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody.
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> . . . .
>
> 18. The method according to claim 17, wherein the anti-CGRP antagonist antibody is:
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> (a) an antibody having a CDR H121 as set forth in SEQ ID NO: 3; a CDR H2 as set forth in SEQ ID NO: 4; a CDR H3 as set forth in SEQ ID NO:5; a CDR L1 as set forth in SEQ ID NO: 6; a CDR L2 as set forth in SEQ ID NO: 7; and a CDR L3 as set forth in SEQ ID NO: 8; or
> (b) a variant of an antibody according to (a) as shown in Table 6.
>
> . . . .
>
> 21. The method according to claim 17, wherein the anti-CGRP antagonist antibody comprises a VH23 domain comprising SEQ ID NO: 1 and VL domain comprising SEQ ID NO: 2.[8]

Lilly's accused product is Galcanezumab, also an anti-CGRP antibody. Galcanezumab is marketed under the brand name Emgality® for treating episodic cluster headaches.[9] The court found that Galcanezumab was not equivalent to the claimed antibody. The court noted that although Galcanezumab has a function similar to the claimed antibody (binding to CGRP and blocking CGRP from engaging with its receptor), Galcanezumab has substantially different sequences (sequence similarity is only 29% in the CDRs). The heavy chain of the closest variant disclosed in Teva's patent shares only 52.5% similarity with Galcanezumab, and Teva's antibody G1 has 50.8% and 64.5% sequence identities. The other differences include that Galcanezumab binds to the mid-region of CGRP.

In contrast, the antibody described in Teva's patent, G1, binds to the C-terminal, and Galcanezumab also binds to CGRP five times more rapidly. Thus, the court found that Lilly's commercialization of Galcanezumab did not infringe the claims asserted by Teva under DOE. Therefore, the court granted Eli Lilly's partial motion for summary judgment for non-infringement.[10]

Notably, the court rejected Teva's arguments that the key inquiry is not whether the amino acid sequences are different but whether the differences matter in the claimed method, *i.e.*, treating headaches. Teva argues that although there is a difference in amino acid sequences between Galcanezumab and the sequences of the patented antibodies, the differences do not matter when used in a method of treating headaches. The court said Teva's argument is "a bridge too far" and that Teva's equivalents argument "would read the amino acid sequence limitation out of claims 18 and 21. [This would] effectively expand the scope of that limitation to

encompass any amino acid sequence in a full-length antibody that has the effect of sufficiently antagonizing CGRP."[11]

II. Legal theories barring the application of DOE to antibody claims

Since the Lilly court concluded that there are no equivalents based on the application disclosure alone, it did not reach other legal theories that bar the application of DOE. However, various legal theories, for example, prosecution estoppel, disclosure-dedication rule, and specific exclusion principle, have been applied to bar the application of DOE in other antibody cases.

Prosecution estoppel

Narrowing amendments made during prosecution raise a rebuttable presumption of surrender "of the territory between the original claim and the amended claim."[12] This presumption can only be overcome if "the equivalent [was] unforeseeable at the time of the application; the rationale underlying the amendment [bore] no more than a tangential relation to the equivalent in question; or there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question."[13]

This amendment-based prosecution estoppel often creates a significant hurdle for antibody patent owners trying to assert DOE. In *Scantibodies Laboratory, Inc. v. Immutopics, Inc.*,[14] the patentee's representative claim is directed to an antibody that binds to a specific region in the parathyroid hormone (PTH).[15] The court found that the accused infringer's product was not equivalent to the claimed antibody because it binds to a different region in the PTH and has a higher affinity. The court also found that the antibodies binding to different PTH epitopes were not unforeseeable at the time of drafting and the prosecution history estoppel bars applying DOE because an amendment was filed changing from "comprise" to "consist of" the specific epitope sequence after an examiner interview.

Similarly, in *UCB, Inc v. Yeda Research & Development Co., Ltd.*,[16] the patentee (Yeda)'s claimed a monoclonal antibody that specifically binds a human cytotoxin with specific features.[17] The court construed the term "monoclonal antibody" to mean "a homogenous population of a single type of antibody produced via hybridoma and not including chimeric or humanized antibodies" and found that the accused product is a humanized antibody, not a monoclonal antibody as claimed.[18] The court then deemed that the patentee surrendered the subject matter of the humanized antibody (having otherwise similar features to the claimed monoclonal antibody) because the patentee canceled claims directed to chimeric and humanized antibodies during prosecution.[19] The court thus granted the accused infringer UCB's summary judgment of non-infringement and held that UCB did not infringe the claim under DOE.

Disclosure-dedication and specific exclusion

The disclosure-dedication rule states that when a patent drafter discloses but declines to claim subject matter, the patent drafter's action then dedicates that unclaimed subject matter to the public. The patent owner

cannot assert DOE to recapture the subject matter deliberately left unclaimed.[20]

The specific exclusion principle refers to a scenario where the accused equivalent was criticized in the specification or prosecution and then not claimed. *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, explained that the specific exclusion principle applies when the patentee defines the claim "in a way that clearly excluded certain subject matter, the patent implicitly disclaimed the subject matter that was excluded and thereby barred the patentee from asserting infringement under the doctrine of equivalents."[21]

The disclosure-dedication rule and the specific exclusion principle were applied to bar application of DOE in *Morphosys AG v. Janssen Biotech, Inc.*[22] In that case, the disputed claim is an isolated human antibody that specifically binds to an epitope of CD38 (SEQ ID NO: 22). The accused product is a humanized antibody that binds to CD38.[23] The court construed that a humanized antibody is not a human antibody.[24] The court reasoned that since the patentee disclosed both humanized antibodies and human antibodies in the application but claimed only human antibodies, the disclosure-dedication rule bars the patentee from asserting that the claim also covers humanized antibodies under DOE.[25] The court found that the humanized antibody and human antibody are mutually exclusive; thus, by claiming only human antibodies, the patentee excludes claims directed to humanized antibodies under the specific exclusion principle.[26]

III. Conclusion

Although courts have applied DOE in other biologics cases, such as *Ajinomoto Co., Inc. v. ITC*,[27] we have yet to see successful application of DOE in antibody cases. The lack of application of DOE in antibody cases is not surprising because the U.S. Supreme Court prohibits using DOE to enlarge a patent beyond the scope of its claims as allowed by the USPTO.[28] The claim scope permitted by the USPTO has been narrowed, limiting antibodies to specific sequences.

Teva v. Eli Lilly indicates that attempts to rely on DOE to broaden the protection through the "backdoor" to the extent that essentially vitiates the limitation of sequence requirements would be unsuccessful. With that said, DOE is a *fact-intensive inquiry*, the ultimate decision on whether DOE applies will depend on the specific facts of each case. As more companies patent their antibody innovations and assert patented claims to protect their investment in this critical therapeutic area, future court decisions could shed additional light on what circumstances DOE may (or may not) be applied in antibody cases.

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Footnotes

[1] Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, at *40 (1997).

[2] Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605 (1950).

[3] No. 18-cv-12029-ADB, 2022 WL 4824318, at *1 (D. Mass. Oct. 3, 2022)

[4] *Id.* at *18 (citing Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 866-67 (Fed. Cir. 2017)).

[5] *Id.*

[6] *Id.* at *16. It is noted that Lilly challenged these three patents before the PTAB, and the PTAB upheld all claims as patentable over the prior art references cited by Lilly. Id. at *6.

[7] *Id.* at *3.

[8] 2022 WL 4824318, at *3, *16 (second alteration in original) (quoting U.S. Pat. No. 8,586,045).

[9] Emgality is the only therapeutic antibody approved by the FDA to treat episodic cluster headaches.

[10] *Id.* at *24.

[11] *Id.* at *18-19.

[12] Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 740 (2002).

[13] *Id.* at 740-41.

[14] 374 F. App'x 968 (Fed. Cir. 2010).

[15] A substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone wherein said initial peptide sequence consists of VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:3), and wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody.

[16] 117 F. Supp. 3d 755 (E.D. Va. 2015).

[17] A monoclonal antibody that specifically binds a human cytotoxin having a molecular weight of about 17,500 as determined by polyacrylamide gel electrophoresis, said cytotoxin being obtainable from stimulated human monocytes, said cytotoxin being further characterized by exhibiting a cytotoxic effect on cycloheximide-sensitized. SV-80 cells and by being obtainable in a state of enhanced purity by adsorption of the cytotoxin from an impure preparation onto controlled pore glass beads and subsequent desorption of the cytotoxin in a state of enhanced purity.

[18] 117 F. Supp. 3d at 774 (citation omitted).

[19] *Id.* at 779.

[20] Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, 1424 (Fed. Cir. 1997) (citing Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997)) (applying DOE in this scenario would "conflict with the primacy of the claims in defining the scope of a patentee's exclusive rights").

[21] 242 F.3d 1337, 1346 (Fed. Cir. 2001).

[22] 358 F. Supp. 3d 354 (D. Del. 2019).

[23] The court denied Janssen's summary judgment motion of invalidity based on the lack of written description. *Id.* at 365.

[24] *Id.* at 360.

[25] *Id.* at 362.

[26] *Id.* at 363.

[27] 597 F.3d 1267 (Fed. Cir. 2010).

[28] Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17 (1997).