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Federal Circuit Decides Teva-Lilly Spat for Antibody Compositions and Methods

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On August 16, 2021, the Federal Circuit handed down two rulings related to patents issued to Teva, which involve therapeutic antibodies targeting a calcitonin gene-related peptide ("CGRP"). In both cases, the Federal Circuit affirmed the Patent Trial and Appeal Board ("the Board")'s decisions on inter partes review ("IPR") filed by petitioner Eli Lilly. However, the outcomes in these two rulings were directly opposite for the patent owner Teva: the claims directed to the antibodies[1] were found obvious and invalid, but the claims directed to the methods of treatment using these antibodies[2] were deemed valid.

1. Antibody composition claims found invalid

In Opinion at 15, *Teva Pharmaceuticals International GmbH v. Eli Lilly & Co.*, Nos. 2020-1747, 1748, 1750, (Fed. Cir. Aug. 16, 2021), the Federal Circuit agreed with the Board that the claims directed to humanized CGRP antibodies[3] were obvious because the prior references disclose both the Fab fragment and the full-length of an anti-CGRP monoclonal antibody can block skin blood flow in animal studies. The Federal Circuit held that the prior art supports a motivation to humanize antibodies with the goal of treating human disease.[4] The Federal Circuit also agreed with the Board that any potential safety concerns alleged by Teva were outweighed by Lilly's reliance on actual studies of the CGRP antagonists; the alleged safety concerns would not have deterred or discouraged the combination of prior art teachings to arrive at the claimed invention.[5]

The Federal Circuit also implicitly agreed with the Board that there would have been a reasonable expectation of successfully achieving the claimed invention and that establishing obviousness of the antibody composition claims does not require a showing of a reasonable expectation of successfully using the claimed antibody in the treatment of a disease or condition.[6]

Finally, the Federal Circuit held that Teva failed to establish a nexus between the claims and an asserted secondary consideration, a licensing agreement and the mere existence of the license is insufficient to overcome the conclusion of obviousness.[7] The Court thus affirmed the Board's decision that Teva's claims directed to a humanized anti-CGRP antagonist antibody are invalid.

2. Method claims upheld

In Opinion, *Eli Lilly & Co. v. Teva Pharmaceuticals International GmbH*, Nos. 2020-1876, 1877, 1878 (Fed. Cir. Aug. 16, 2021),—in contrast to its disposition of Teva's antibody composition claims—the Federal Circuit affirmed the Board's decision that claims directed to methods of treating migraine-related conditions using the anti CGRP antagonist antibodies were valid.[8] The primary prior art that Lilly relied on for the obviousness contention discloses clinical trial data proving the efficacy of a small molecule, non-peptide, CGRP-receptor antagonist in the treatment of migraine.[9] The Federal Circuit deemed that the claim preamble reciting specific purpose of treating migraine-related symptoms is a claim limitation.[10] Although the Court agreed with Lilly that there was motivation to combine the teachings of the cited references, the Court agreed with the Board that the prior art's disclosure of the small molecule compound's ability to block the CGRP receptor does not provide a reasonable expectation of success of administering an anti-CGRP antibody to treat migraine-related conditions.[11] The Court also noted that the prior art reference did not provide data showing that a full length anti-CGRP antibody could reach the synaptic cleft, the site of action for immunoblockade, which is required to achieve inhibition of endogenous CGRP in vivo.[12] The Federal Circuit thus determined that that Lilly has failed its burden to prove there is reasonable expectation of success that performing the recited method would bring about the recited result. The Court then affirmed the Board's decision to uphold the patentability of the method claims.[13]

3. Take-away:

While antibody composition claims are highly desirable, the bar to patentability of these claims is high. It is relatively easy for a challenger to find motivation to combine references to produce an antibody when there is some sort of teaching of potential benefit and when the antigen is well-known. There is often little to prevent a challenger from asserting that there is reasonable expectation of success to produce these antibodies. In contrast, treating a patient using antibodies for therapeutics purposes is still considered unpredictable, and thus, claims directed to methods of treatment using these antibodies are easier to defend.

Patent owners should always try to include different types of claims to maximize the likelihood of success in obtaining protection of antibody-related inventions. It is highly desirable to include both antibody composition claims and method of treatment claims in therapeutic antibody applications. When claiming antibodies, defining the antibodies by structure rather than by epitopes may avoid running afoul of the nonobviousness and/or other patentability requirements[14]. When claiming method of treatment, consider including the intended purpose of the treatment in at least some claims.

Petitioners (challengers) should focus their efforts on invalidating antibody composition claims if resources are limited. It is also advisable to assess the similarity between the prior art teaching and the claimed methods to gauge if there is a reasonable expectation of success in any litigation strategy.

[1] Three antibody composition patents (U.S. Patent Nos. 9,340,614, 9,266,951, and 9,890,210) were challenged in *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01422 (P.T.A.B. decided Feb. 18, 2020), *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01423 (P.T.A.B. decided Feb. 18, 2020), and E*li Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01425 (P.T.A.B. decided Feb. 18, 2020).

[2] Three method of treatment patents (U.S. Patent Nos. 8,586,045, 9,884,907, and 9,884,908) were challenged in *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01710 (P.T.A.B. decided Feb. 18, 2020), *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01711 (P.T.A.B. decided Feb. 18, 2020), and *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, IPR2018-01712 (P.T.A.B. decided Feb. 18, 2020).

[3] The representative claims of the challenged patents are:

claim 1 of the '614 Patent: a human or humanized monoclonal anti-CGRP antagonist antibody that preferentially binds to human α-CGRP as compared to amylin;

claim 1 of the '951 Patent: a human or humanized monoclonal anti-CGRP antagonist antibody that (1) binds human α-CGRP and (2) inhibits cyclic adenosine monophosphate (cAMP) activation in cells;

claim 1 of the '210 Patent: a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist anti-body, comprising: two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and two light chains, each light chain comprising three CDRs and four framework regions; wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43.

[4] Opinion at 12, T*eva Pharms*., No. 20-1747.

[5] *Id*. at 13.

[6] The Federal Circuit did not object to the Board's conclusion that there was a reasonable expectation of success of practicing the claimed humanized antibody.

[7] *Id*. at 23.

[8] The representative claims of the challenged patents are:

claim 1 of the 045 Patent: a method for reducing incidence of or treating at least one vasomotor symptom in an individual, comprising administering to the individual an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody;

claim 1 of the '907 Patent: a method for treating headache in an individual, comprising: administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising: two human IgG heavy chains, each heavy chain comprising three complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and two light chains, each light chain comprising three CDRs and four framework regions; wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO:43;

claim 1 of the '908 Patent: a method for treating headache in an individual, comprising: administering to the individual an effective amount of a humanized monoclonal anti-Calcitonin Gene-Related Peptide (CGRP) antagonist antibody, comprising: two human IgG heavy chains, each heavy chain comprising three

complementarity determining regions (CDRs) and four framework regions, wherein portions of the two heavy chains together form an Fc region; and two light chains, each light chain comprising three CDRs and four framework regions; wherein the CDRs impart to the antibody specific binding to a CGRP consisting of amino acid residues 1 to 37 of SEQ ID NO:15 or SEQ ID NO: 43, and wherein the antibody binds to the CGRP with a binding affinity (KD) of about 10 nM or less as measured by surface plasmon resonance at 37ºC.

[9] Opinion at 6, *Lilly*, No. 2020-1876.

[10] *Id*. at 14.

[11] *Id*. at 27.

[12] *Id*.

[13] *Id*. at 31.

[14] Claiming antibodies by epitopes only may also be deemed lacking written description; these issues are not reviewable by IPR, but can be reviewed in other venues.