

Divided Infringement After Eli Lilly V. Teva

By Eric Steffe, Marsha Rose Gillentine and Brenda Crabtree, Sterne Kessler Goldstein & Fox PLLC

Law360, New York (April 18, 2017, 11:57 AM EDT) --

The rapidly growing field of precision medicine involves classifying individuals through diagnostic testing into subpopulations that differ in their susceptibility to a particular disease. These diagnostic tests are often performed by various people, including health care professionals who collect samples and laboratory personnel who assay the samples and generate data. The involvement of multiple people during the testing process is potentially problematic for patent owners in view of case law holding that direct infringement cannot be based on actions divided among different people.[1]

In *Eli Lilly v. Teva Parenterals Medicines Inc.*,[2] the Federal Circuit addressed divided infringement in the context of the pharmaceutical industry for the first time following its decision in *Akamai Technologies Inc. v. Limelight Networks Inc.*[3] In *Eli Lilly*, the Federal Circuit also clarified the “label ... in its entirety” language referred to in *Bayer Schering Pharma AG v. Lupin, Ltd.*,[4] by agreeing that both physician prescribing information and patient information can be used as evidence to show direct and induced infringement.[5] The Federal Circuit’s decision provides insight to companies engaged in patenting precision medicine.

Overview of *Eli Lilly v. Teva Parenterals Medicines Inc.*

In August 2010, Eli Lilly & Co. obtained U.S. Patent No. 7,772,209 to methods for administering pemetrexed disodium (“pemetrexed,” brand name Alimta) where the patient is pretreated with folic acid and vitamin B12.[6] Claim 1 of the ’209 patent is representative:

1. A method of administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium,

wherein the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.[7]



Eric Steffe



Marsha Rose Gillentine



Brenda Crabtree

The defendants informed Eli Lilly they had submitted abbreviated new drug applications for generic versions of Alimta. Following issuance of the '209 patent, the defendants sent Eli Lilly further notices that the '209 patent was invalid, unenforceable, or would not be infringed.

Eli Lilly filed suit in the United States District Court for the Southern District of Indiana alleging the defendants' new generic products with accompanying literature would infringe the '209 patent under 35 U.S.C. § 271(e)(2). Eli Lilly argued the defendants' products would be administered after pretreatment with folic acid and vitamin B12, as required by two sections found in the defendants' proposed product labeling — the physician prescribing information and the patient information. According to Eli Lilly, these two sections include instructions to doctors to direct patients to take, or patients themselves to take, folic acid and vitamin B12 prior to treatment with pemetrexed. Specifically, the physician prescribing information section states, in relevant part:

Instruct patients to initiate folic acid 400 [µg] to 1000 [µg] orally once daily beginning 7 days before the first dose of [pemetrexed]....[]

Instruct patients on the need for folic acid and vitamin B12 supplementation to reduce treatment related hematologic and gastrointestinal toxicity....[]

And the Patient Information section states, in relevant part:

To lower your chances of side effects of [pemetrexed], you must also take folic acid ... prior to and during your treatment with [pemetrexed]. []

It is very important to take folic acid and vitamin B12 during your treatment with [pemetrexed] to lower your chances of harmful side effects. You must start taking 400–1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of [pemetrexed]....[][8]

During this time, litigation between Akamai Technologies Inc. and Limelight Networks Inc. was also ongoing. Following the U.S. Supreme Court's holding that liability for inducement requires a finding of direct infringement,[9] the Federal Circuit considered the standards for direct infringement and clarified the scope of actions that may lead to liability in divided-infringement cases.[10] Regarding divided infringement, the Federal Circuit found a single entity is responsible for the performance of method steps when that entity "directs or controls' others' performance," or when "the actors form a joint enterprise." [11] Further, directing or controlling others' performance includes circumstances in which an alleged infringer (1) "conditions participation in an activity or receipt of a benefit' upon performance of a step or steps of a patented method," and (2) "establishes the manner or timing of that performance." [12]

The district court in Eli Lilly applied the Federal Circuit's decision in Akamai V and held, among other things, that although no single actor performs all steps of the '209 patent's asserted claims, direct infringement could be attributed to physicians, and the defendants were liable for inducing that infringement.[13]

The Federal Circuit affirmed the district court, noting physicians directly infringed the '209 patent by conditioning receipt of a benefit — receiving pemetrexed treatment — on patients' taking a specified dose of folic acid at a specified time (daily).[14] The Federal Circuit rejected Defendants' argument that "mere guidance or instruction is insufficient to show 'conditioning' under Akamai V," finding that conditioning "does not necessarily require double-checking another's performance or making

threats.”[15] The Federal Circuit also rejected the defendants’ argument that “an actor can only condition the performance of a step ‘by imposing a legal obligation to do so, by interposing that step as an unavoidable technological prerequisite to participation,’” or both.[16]

Regarding induced infringement, the Federal Circuit found that Eli Lilly met its burden of proving specific intent, noting that “the intent for inducement must be with respect to the actions of the underlying direct infringer, here physicians.”[17] The Federal Circuit found that the defendants’ proposed labeling “would inevitably lead some physicians to infringe.”[18]

Strategic Considerations After Eli Lilly

After Eli Lilly, establishing induced infringement of patents with claims incorporating diagnostic steps against competing companies seeking to market a generic or biosimilar product may turn on (1) whether the competing company includes the diagnostic test on its product label, and (2) whether individuals performing the diagnostic testing are under the direction of the treating physician.

Competing companies who market small molecule generic drugs typically do not employ field representatives to promote the company’s product. Therefore, patentees must rely on the competitors’ product labeling as evidence of infringement. Although competing companies seeking to market biosimilar drugs will likely employ field representatives to promote their products, the product label will also be a vital piece of evidence for demonstrating infringement for biologicals. Based on the Federal Circuit’s holding in Eli Lilly, it is now clear the entire label may be used as evidence of inducement.

A competitor must certify to the U.S. Food and Drug Administration that its product label is the same as the reference product's labeling except for certain approved changes.[19] Thus, patentees with drugs in clinical trials should consider including instructions for carrying out the diagnostic test in its product labeling prior to patient treatment. For example, the physician prescribing information could “instruct laboratory personnel to perform x testing before treatment can be administered to the patient.” And because the language in the labeling must rise above mere suggestion, words such as “test must be performed” may be beneficial for patentees.[20] Using mandatory language appearing on product labeling significantly increases the likelihood the language will also appear on a competitor’s label.

In Eli Lilly, physicians directed and controlled patients’ actions by conditioning receipt of a benefit on patients’ taking a specified dose of folic acid at a specified time. The Federal Circuit noted that “reduction in toxicities” was not the benefit to be conditioned, however, treatment with pemetrexed was the benefit.[21] In cases involving laboratory testing rather than patient compliance, the actions of laboratory staff rather than patients are at issue when assessing whether there was an underlying direct infringement. In such cases, patentees need to consider what language needs to be included in product labeling to better ensure that physicians will either “direct and control” laboratory personnel or “form a joint enterprise.”[22] If the laboratory staff and physicians are employed by the same organization, a joint enterprise argument may be possible, which goes beyond the scope of this article. But if the laboratory staff are employed at an external organization, an argument can be made under Eli Lilly that physicians condition receipt of a benefit — payment for testing services — on the laboratory staff’s performance of a specific diagnostic test within a specified time.

In sum, for companies seeking FDA approval of new drug products, Eli Lilly highlights the importance of integrating patent strategy and the language chosen for the product labeling.

Eric K. Steffe and Marsha Rose Gillentine, Ph.D., are directors and Brenda G. Crabtree is an associate at Sterne Kessler Goldstein & Fox PLLC in Washington, D.C.

The opinions expressed are those of the author(s) and do not necessarily reflect the views of the firm, its clients, or Portfolio Media Inc., or any of its or their respective affiliates. This article is for general information purposes and is not intended to be and should not be taken as legal advice.

[1] See, e.g., *Limelight Networks, Inc. v. Akamai Techs., Inc. (Akamai III)*, 134 S. Ct. 2111 (2014).

[2] 845 F.3d 1357 (Fed. Cir. 2017).

[3] 797 F.3d 1020 (Fed. Cir. 2015).

[4] 676 F.3d 1316, 1324 (Fed. Cir. 2012).

[5] *Eli Lilly*, 845 F.3d at 1363-69.

[6] *Id.* at 1361-62.

[7] '209 patent, col. 10 ll. 55–65 (emphasis added).

[8] *Eli Lilly*, 845 F.3d at 1364.

[9] See *Akamai III* at 2115.

[10] See *Akamai Technologies, Inc. v. Limelight Networks, Inc. (Akamai V)*, 797 F.3d 1020 (Fed. Cir. 2015) (en banc) (per curiam).

[11] *Akamai V* at 1022.

[12] *Id.* at 1023 (emphasis added).

[13] See *Eli Lilly*, 845 F.3d at 1363.

[14] *Id.* at 1365-68.

[15] *Id.* at 1366.

[16] *Id.* at 1366-67.

[17] *Id.* at 1368.

[18] *Id.* at 1369.

[19] See 21 C.F.R. § 314.94(a)(8); U.S. Dept. of Health & Human Servs., *Labeling for Biosimilar Products, Draft Guidance for Industry* (March 2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>.

[20] See, e.g., *Eli Lilly*, 845 F.3d at 1368-69.

[21] *Id.* at 1365.

[22] *Id.* at 1364.

All Content © 2003-2017, Portfolio Media, Inc.