IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY,
Petitioner,

v.

TEVA PHARMACEUTICALS INTERNATIONAL GMBH,
Patent Owner.

CASE IPR2018-01423
Patent 9,266,951

PATENT OWNER'S SURREPLY

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I. Introduction

Teva's Patent Owner Response ("POR") exposed multiple infirmities that defeat Lilly's obviousness case. Teva demonstrated that Lilly's principal references—Tan 1995 and Wimalawansa—would not have motivated a POSA to develop an anti-CGRP antibody for human therapeutic use. Tan 1995, a basic research paper attempting to "prob[e] the role of CGRP as an endogenous vasodilator" in rats, reported that its full-length anti-CGRP antibody failed to show immunoblockade in a rat saphenous nerve assay. Wimalawansa—far from suggesting humanizing anti-CGRP antibodies, as Lilly argues—expressly conveys to a POSA that "[c]learly, more data from carefully designed studies are necessary before … humanized anti-CGRP monoclonal antibodies … can be evaluated as therapeutic agents." And Lilly has not shown that such data existed prior to 2005.

Unable to overcome these and other fatal defects, Lilly accuses Teva of "impermissibly reading safety and efficacy requirements into the claims." But it was Lilly who premised its Petition on *human therapeutic use*. Teva rebutted Lilly's arguments by, *inter alia*, showing that Lilly failed to consider *safety*, and fell short of demonstrating *efficacy*.

Rather than considering the prior art as a whole, as it must, Lilly, through hindsight, selectively cherry-picks references Lilly believes support its arguments, while ignoring references that undermine them. Even worse, on cross-examination

Dr. Charles and his replacement, Dr. Balthasar[1], distanced themselves from unfavorable portions of Lilly's *own* references upon which they themselves relied. Specifically, these experts refused to consider teachings that call into question the safety of long-term (as with an antibody) inhibition of CGRP, the body's most potent vasodilator. Given that Lilly constructed its obviousness case on a therapeutic utility, the lack of safety and efficacy in its evidence cannot be ignored.

On Reply, Lilly now pivots from its initial "human therapeutic use" arguments, focusing instead on the mere "potential" for therapeutic use. But Lilly cannot re-craft its challenge on Reply to attempt to rehabilitate its Petition. *Henny Penny Corp. v. Frymaster LLC*, No. 18-1596 (Fed. Cir. 2019).

To support its new rationale, Lilly again cherry-picks isolated, out-of-context phrases to repaint the field as of 2005. For example, to support the alleged *in vivo* effectiveness of Tan's C4.19 antibody, Lilly cites to Teva's Dr. Ferrari. But Dr. Ferrari's testimony referred to Tan's Fab' fragment, not full-length C4.19. And Lilly's new arguments that carcass studies support speculation that Tan's antibody would eventually reach its site of action given more time also fail because

[1] Teva discredited a number of Dr. Charles' opinions, and showed him to be unqualified to offer them. POR, 3-4. On Reply, Lilly submitted the declaration of a new expert Dr. Balthasar in an effort to repair Dr. Charles' failed opinions.

"***assignment of a site*** … of antibody localization ***was not possible***." [2]

Similarly, Lilly's speculation about "increased dose" goes squarely against safety concerns regarding long-term CGRP ligand antagonism, which would remove CGRP's protective role during ischemic events, where the risk of stroke and heart attacks are elevated. This is important because migraineurs were known to have increased risk of these life-threatening conditions.

Lilly also fails to rebut Teva's strong showing of numerous indicia of non-obviousness, which support confirming the challenged claims. In short, Teva's Response demonstrates that Lilly's Petition fails to show that the claimed humanized antibodies would have been obvious. Lilly's Reply does not salvage its Petition.

II. Lilly premised its case on the "therapeutic utility" of anti-CGRP antibodies; it should be held to this rationale.

Lilly provided only one reason for developing a humanized anti-CGRP antibody: human therapeutic use. Petition, 13-14, 26-30, 32-33, 34-35. Lilly specifically argued the reason for humanizing a murine antibody was to retain "the antibody's therapeutic utility" "in humans." *Id.*, 34-35. By doing so, Lilly (not Teva) read "safety and efficacy requirements into the claims." Under a similar challenge to composition of matter claims, as here, the Board held the petitioner to

[2] Emphasis added throughout unless otherwise noted.

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