UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
APOTEX INC., and APOTEX CORP.,
EMCURE PHARMACEUTICALS LTD.,
HERITAGE PHARMA LABS INC.,
HERITAGE PHARMACEUTICALS INC.,
GLENMARK PHARMACEUTICALS, INC., USA,
GLENMARK HOLDING SA,
GLENMARK PHARMACEUTICALS, LTD., MYLAN LABORATORIES LIMITED, TEVA PHARMACEUTICALS,
FRESENIUS KABI USA, LLC, and WOCKHARDT BIO AG
Petitioners,

v.

ELI LILLY & COMPANY,
Patent Owner.

Case No. IPR2016-00318[1]
Patent No. 7,772,209

PATENT OWNER'S SUR-REPLY[2]

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[1] Cases IPR2016-01429, IPR2016-01393, and IPR2016-01340 have been joined with the instant proceeding.

[2] Pursuant to the Board's authorization (*see* Ex. 2131), a combined sur-reply, identical except for the caption, case number header, and certificate of service, is being filed in IPR2016-00237, IPR2016-00240, and IPR2016-00318.

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In its Patent Owner Responses, Lilly described how the person of ordinary skill in the art (POSA) would have expected folic acid and vitamin B_{12} pretreatment to reduce pemetrexed's efficacy, and therefore would not have been led to the claimed invention. Tellingly, in their Replies, Petitioners do not contest that the POSA would have been concerned with pemetrexed's efficacy in addition to its toxicity. Instead, they put forward a raft of new arguments about why the POSA allegedly would have expected the claimed regimen not to reduce efficacy. They also focus on how Lilly—after the priority date and with knowledge of the invention—advocated for its own invention in publications and to the FDA. For the reasons discussed below, Petitioners' arguments are *post hoc* rationalizations for the invention that constitute improper hindsight reasoning, fail to rebut Lilly's points, and cannot support Petitioners' claims of obviousness.[3]

I. Petitioners' New Biochemical Theories Arguing that Folate Is Not an "Antidote" Only Emphasize the Nonobviousness of the Invention

Having largely ignored in their Petitions the expected negative impact of the

[3] Consistent with the Board's direction, this brief responds only to improper new Reply arguments. Petitioners also made arguments, such as attacks on the credibility of Lilly's witnesses, that are meritless but do not fall within the Board's direction. As necessary, Lilly will respond to such arguments at oral argument.

claimed vitamin pretreatments on pemetrexed's efficacy, Petitioners now advance several theories to argue that folic acid and vitamin B_{12} do not act as antidotes to pemetrexed. Critically, the question is not whether, today, Petitioners' experts can come up with a scientific hypothesis as to how folic acid and vitamin B_{12} pretreatment might be able to reduce pemetrexed's toxicity without harming efficacy. We know today that there must be some explanation, as we now know from experience that Dr. Niyikiza's invention in fact works. But that is always true for successful inventions. The question for obviousness, however, is whether *the prior art* taught or suggested any such rationale which would make Dr. Niyikiza's invention obvious to the POSA. *E.g.*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012).

There are no such teachings, and, in any event, Petitioners' new scientific arguments are unavailing.

A. The Potency of Pemetrexed's Enzyme Inhibition Would Not Have Addressed the POSA's Efficacy Concerns

Neptune argues that folic acid does not act as pemetrexed's "antidote" by observing that pemetrexed is a potent inhibitor of DHFR, the enzyme responsible for converting folic acid to useful "reduced" forms. Neptune Reply 12-14; Neptune Ex. 1077 ¶¶ 19-23; Neptune Ex. 1078 ¶¶ 22-35, 40-46. Accordingly, Neptune argues that because pemetrexed would be expected to completely block DHFR, any folic acid administered in the presence of pemetrexed would never be

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