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 MOTION FOR OBSERVATIONS ON THE DEPOSITION OF PETITIONER SANDOZ'S EXPERT RON D. SCHIFF, M.D.

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

Pursuant to 77 Fed. Reg. 48756, Patent Owner Eli Lilly & Company ("Lilly") submits this motion for observations regarding cross-examination of Petitioner Sandoz's reply declarant Ron D. Schiff, M.D.

Observation 1. Dr. Schiff testified that Farber demonstrated in the 1940s "the principle . . . that folic acid and vitamin B-12 can be administered to patients who are also treated with antifolates for malignancy. And in some cases, the results were better with historical controls than they were if the antifolate was not used or than they were without the B vitamins." Ex. 2136 at 45:10-18. Dr. Schiff further testified that at least by 1959, "there would have been a reason to conclude that vitamin B-12 would have been of interest" in antifolate treatment. *Id.* at 46:15-47:10. This testimony is relevant to Lilly's argument that vitamin B_{12} pretreatment would not have been obvious because over many decades of the use of antifolates and recognition of antifolate toxicity problems, vitamin B_{12} pretreatment was not used, suggesting that its use was not in fact obvious. Paper 36 at 2, 4, 8-9, 34-35.

Observation 2. Dr. Schiff testified that it would "certainly be a mistake to assume that what one found with one antifolate compound would apply exactly to another, which is why someone who's interested in developing pemetrexed for clinical applications would pay the greatest attention to the pemetrexed research leading up to that point and then after that would diverge the study to other

antifolates." Ex. 2136 at 31:5-14. This testimony is relevant because it supports Patent Owner's argument that if (contrary to Patent Owner's position) the POSA were to use folic acid pretreatment with pemetrexed, the POSA would look to a reference such as Hammond, which described a pemetrexed clinical trial, when determining the appropriate dosage of folic acid, rather than to trials of other drugs or doses used in other contexts. Paper 36 at 52.

Observation 3. Dr. Schiff agreed that "it was known in 1999 that pemetrexed['s] clearance is primarily renal [*i.e.*, through the kidneys]." Ex. 2136 at 80:25-81:4. He further agreed that if the POSA believed a drug that was cleared renally were nephrotoxic, the POSA "would expect that you would see increased toxicity from those who had kidney impairment." *Id.* at 82:1-21. This testimony is relevant to Lilly's argument that the POSA would not expect folic acid supplementation to permit a useful escalation of pemetrexed's dose, because (1) dose escalation is not useful without an increase in efficacy; (2) the POSA would expect folic acid to reduce efficacy, thus counteracting any efficacy benefit that might arise from a higher dose; and (3) worse, the Hammond study revealed signs of kidney toxicities at higher doses that would not have been ameliorated by folic acid (or vitamin B_{12}) pretreatment. Paper 36 at 28-29; Ex. 2120 ¶¶ 49, 73-74, 76-82.

Observation 4. Dr. Schiff agreed that "the possibility of dose reductions is a routine part of oncology practice." Ex. 2136 at 87:3-7. This testimony is relevant because it supports Lilly's argument that dose and schedule reductions would have been an obvious way for the POSA to manage any pemetrexed toxicities that might be encountered, and that pemetrexed's toxicities were regarded as tolerable and manageable using "conventional dose and schedule adjustments." Paper 36 at 21-23 (quoting Ex. 1052 at 1194, 1198).

Observation 5. Dr. Schiff testified that the POSA "would not want to do anything to compromise response rates if at all possible." Ex. 2136 at 91:15-92:12. This testimony is relevant to Lilly's argument that the POSA would not have adopted or modified a pemetrexed dosing regimen in a way that compromised pemetrexed's promising efficacy. Paper 36 at 19-23.

Observation 6. Dr. Schiff agreed that "the fact that betaine hadn't been used" to pretreat an antifolate patient was "a contributing factor" that "would cause a person of ordinary skill not to focus on it." Ex. 2136 at 98:21-99:17; *see also id.* at 106:10-17 (stating that Quinn, which discussed the use of betaine to lower homocysteine, "does not propose an alternative that has a track record"). This testimony is relevant because it contradicts Petitioner's argument that the POSA would pretreat pemetrexed patients with vitamin B_{12}, because it had never been

used to pretreat a cancer patient receiving a folate analogue antifolate such as pemetrexed. Paper 36 at 34-35.

Observation 7. Dr. Schiff testified that he "ha[s] a little bit of a hard time thinking of fatigue specifically as a central nervous system toxicity," that fatigue is "very, very nonspecific," and that the POSA "hears complaints about fatigue from virtually every patient in their practice." Ex. 2136 at 121:18-124:12. Dr. Schiff further testified that "the hematologic toxicities as well as gastrointestinal toxicities—by which I would mean things like mucositis, diarrhea, even liver function test elevation—would be of greater concern to the person of ordinary skill than fatigue." *Id.* at 123:16-124:12. This testimony is relevant because it supports the opinion of Dr. Chabner that fatigue is "a common side effect of virtually all cancer treatments," would not be understood as a neurotoxicity, would not have been understood to correlate with homocysteine levels in the Niyikiza abstracts, and would not provide a motivation for the POSA to administer vitamin B_{12}. Ex. 2120 ¶ 129. The testimony is therefore also relevant to Lilly's argument that the slow-onset neurotoxicities that are sometimes observed in cases of severe vitamin B_{12} deficiency (outside the context of antifolate chemotherapy) would not have motivated the POSA to administer vitamin B_{12} pretreatment to patients receiving pemetrexed. Paper 36 at 45.

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