UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
APOTEX INC., APOTEX CORP., TEVA PHARMACEUTICALS,
FRESENIUS KABI USA, LLC, and WOCKHARDT BIO AG
Petitioners,

v.

ELI LILLY & COMPANY,
Patent Owner.

Case No: IPR2016-00240[1]
Patent No. 7,772,209

PATENT OWNER'S MOTION FOR OBSERVATIONS ON THE DEPOSITION OF PETITIONER NEPTUNE GENERIC'S EXPERT W. ARCHIE BLEYER, M.D.

[1] Cases IPR2016-01191, IPR2016-01337, and IPR2016-01343 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 Neptune Generic's reply declarant W. Archie Bleyer, M.D.

Observation 1. Dr. Bleyer testified that in the "homocysteine-to-methionine reaction," "a methyl is removed from 5-methyltetrahydrofolate and place on to homocysteine to create methionine," so "the product of the reaction is you get homocysteine converted to methionine, and you get methyltetrahydrofolate converted to tetrahydrofolate." Ex. 2135 at 50:5-18. Dr. Bleyer further testified that "tetrahydrofolate can be used by the cell to make DNA precursors." *Id.* at 50:19-21. Dr. Bleyer then agreed that "[i]f the cell had methyltetrahydrofolate in it and sufficient B12 to allow the homocysteine-to-methionine reaction to occur, that reaction would go forward whether or not DHFR was blocked by an inhibitor." *Id.* at 52:5-19. This testimony is relevant because it supports Patent Owner's argument that the ability of vitamin B_{12} to release folate is not blocked when DHFR is inhibited. Paper 32 at 26-27. Thus, even if Neptune were correct that the POSA would not expect folic acid to reduce pemetrexed's efficacy because of pemetrexed's ability to block DHFR, the POSA would still expect vitamin B_{12} to reduce efficacy. *Id.*

Observation 2. Dr. Bleyer agreed—in discussing an article by Dr. Sidney Farber (Ex. 2042)—that "Dr. Farber's conclusion that it was the folate that caused

the acceleration phenomenon [*i.e.*, tumor growth] is what gave him the idea for antifolates in the first place." Ex. 2135 at 59:19-24; *id.* at 60:9-17. This testimony is relevant because it supports Patent Owner's argument that the POSA would have been concerned that pretreating with folic acid would have enhanced the growth of the patient's cancer. Paper 32 at 21-22.

Observation 3. Dr. Bleyer agreed that when a vitamin B_{12} deficient patient is administered vitamin B_{12}, "more tetrahydrofolate would be created through the homocysteine-to-methionine reaction." Ex. 2135 at 68:13-17. Dr. Bleyer further agreed that he would "expect that to occur in a significant percentage of the cancer patients you saw because you thought a significant percentage had a vitamin B12 deficiency." *Id.* at 68:19-69:1. This testimony is relevant because it supports Patent Owner's point that administering vitamin B_{12} can make more folate available by converting inactive folate to active folate, and thereby dramatically reduce pemetrexed's efficacy. Paper 32 at 6-8, 22-23. The testimony is also relevant because it contradicts Neptune's argument that the "methyl trap"—*i.e.*, what Neptune describes as a situation in which "administering vitamin B_{12} to a B_{12}-deficient patient can potentially cause usable folate to be released"—is "very rare." Paper 47 at 27.

Observation 4. Dr. Bleyer testified:

> Q. Okay. And second sentence says, "Folate therapy will reliably reduce plasma homocysteine levels; however, this would also rescue cells from the cytotoxic effects of methotrexate." Have I read that correctly?
>
> A. You did.
>
> Q. And would the person of ordinary skill have agreed with that?
>
> A. Because it is in this excellent journal, they would tend to agree with that. Let me read it again. Yes.

Ex. 2135 at 121:22-122:8. This testimony is relevant because it supports Patent Owner's point that administering folic acid to a patient receiving an antifolate would have reduced the antifolate's efficacy. Paper 32 at 20-32. This testimony also undermines Petitioner's assertion that folic acid administration would not affect pemetrexed's efficacy. Paper 47 at 12-14.

Observation 5. Dr. Bleyer testified:

> Q. Okay. I want to make sure I understand, because there was a lot of parts of that. So which -- what are you relying on to say that you're starting to see -- I think you said, "kidney function is beginning to suffer," then later you said, "beginning to go into renal failure." What are you talking about?
>
> A. The sentence that you brought to my attention that seven of 15 patients develop decreased creatinine clearance, which is the classic sign of renal dysfunction, more than half of the patients, seven of 15 patients

develop renal function. That's a high rate, and those are the patients who had an elevation of all three vitamins, and I think a POSA would then worry -- suspect that the predictor is no longer as effective because now the drug is causing more problems, including the increased toxicity just from causing renal dysfunction.

Ex. 2135 at 130:22-131:16. Dr. Bleyer further testified:

Q. So this isn't talking about their baseline level of creatinine. It is referring to a drug-related toxicity as including a decrease in creatinine clearance, which is indicating that it's due to the drug; correct?

A. Now that I'm reading it again with you, I think the first interpretation was more correct.

Q. Right.

A. Yes.

Q. All right? And so the patients -- let me just -- I want to make sure I have this correct. The decrease in creatinine clearance is an indication of a developing kidney problem, you said?

A. Yes.

Q. Okay. And the -- you are saying the developing kidney problem was due to the increased doses of the drug; is that what you said initially?

A. I think I referred to the higher doses used in this report up to 925, which are known at the higher levels to cause kidney toxicity.

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