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: IPR2016-00237[1]
Patent No. 7,772,209

PATENT OWNER'S MOTION FOR OBSERVATIONS ON THE DEPOSITION OF PETITIONER NEPTUNE GENERIC'S EXPERT JOEL B. MASON, M.D.

[1] Cases IPR2016-01190, IPR2016-01335, and IPR2016-01341 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 Joel B. Mason, M.D.

Observation 1. Dr. Mason testified:

> Q. Let me ask a different question. In a patient who is vitamin B12 replete, adding more vitamin B12 isn't going to affect homocysteine levels.
>
> * * *
>
> A. Again, let me just make sure I understood the question. So in a B12 replete patient, adding additional B12 is not going to further lower homocysteine levels; is that what you're saying?
>
> Q. Well, is it going to have any effect on homocysteine levels?
>
> A. In general, as far as I can recollect, it will not.

Ex. 2134 at 26:24-27:13 (objection omitted). This testimony is relevant to Lilly's argument that, in order for vitamin B_{12} to have a beneficial effect on toxicity, it would have to concomitantly release reduced folates that would counteract pemetrexed's efficacy, and thus would not have been obvious to administer. Paper 33 at 2, 6-9, 17-22, 25. This testimony also is relevant because it demonstrates that Dr. Mason's opinions are premised upon an understanding that the vitamin B_{12} would not be expected to have any effect in patients who are not vitamin B_{12} deficient, a position that contradicts the statement in Neptune's Reply that the

POSA would be motivated to administer vitamin B_{12} only to patients who are *not* vitamin B_{12} deficient. Paper 48 at 27.

Observation 2. Dr. Mason testified:

> Q. A patient walks into a doctor's office as of 1999 and is given vitamin B12.
>
> A. Yeah.
>
> Q. Whether or not that patient shows signs of vitamin B12 deficiency in an MMA study, for example, or some other biochemical assay, the person of ordinary skill doesn't know for sure whether that administration of vitamin B12 is going to make more tetrahydrofolate available.
>
> * * *
>
> A. I think that there are insufficient studies for either myself or the POSA to know whether the actual availability of THF to the cell, okay, to that hypothetical patient's cells, would be increased by the administration of vitamin B12.

Ex. 2134 at 33:5-33:21 (objection omitted). Dr. Mason further testified:

> Q. If vitamin B12 were administered to a patient and that has the effect of releasing some tetrahydrofolate, the person of ordinary skill in the art would not have a way to quantify how much would be released.
>
> * * *

A. The POSA would in all likelihood not have the appropriate tests available to make that determination.

Id. at 36:10-18 (objection omitted). This testimony is relevant to Lilly's argument that the administration of vitamin B_{12} to a patient may release an unpredictable amount of reduced folate, which would then be available to cancer cells to reverse the efficacy of pemetrexed and/or accelerate cancer growth; the POSA therefore would have seen vitamin B_{12} pretreatment as "worrisome," not obvious. Paper 33 at 20-22.

Observation 3. Dr. Mason testified that "if you were to give a patient taking pemetrexed a reduced folate such as leucovorin or tetrahydrofolate, that could have the effect of negating its effect" and that "administration of a reduced form of folate such as leucovorin, which is 5-formyltetrahydrofolate, would bypass the block that otherwise is seen by folic acid because folic acid needs that DHFR activity to be converted into a form that can be utilized by the cell." Ex. 2134 at 49:12-25. This testimony is relevant to Lilly's argument that the administration of folic acid pretreatment (which has the effect of increasing the supply of reduced folates, even if Neptune is correct that DHFR blocks the reduction of folic acid once pemetrexed is administered), and the administration of vitamin B_{12} (which releases tetrahydrofolate, a reduced folate), would have been understood to undermine the effect of pemetrexed on cancer cells and thus reduce pemetrexed's

efficacy, thus rendering folic acid and vitamin B_{12} pretreatment non-obvious. Paper 33 at 18-29.

Observation 4. Dr. Mason testified that, if a patient were pretreated with folic acid, "[a] large part" of that folic acid "would be converted to a reduced form." Ex. 2134 at 95:4-8, 100:14-18. Dr. Mason further testified that the enzyme DHFR "can act in a matter of seconds on folic acid" and is "a reaction that potentially can move along very quickly." *Id.* at 95:21-96:23. Thus, if folic acid pretreatment were administered to a patient beginning two days before pemetrexed, "[t]here certainly would be a dramatic drop in homocysteine over the course of those two days." *Id.* at 97:18-99:11. This testimony is relevant because it undermines Dr. Mason's assertion that "blockage of DHFR by pemetrexed impairs the ability of folic acid to be effectively utilized within the folate metabolic network by preventing folic acid (unusable by the body in DNA synthesis) from being reduced to its useable form, tetrahydrofolate," which is a reason Dr. Mason asserts folic acid pretreatment would not impair pemetrexed's efficacy. *See* Ex. 1078 ¶ 46. In the case of folic acid pretreatment, to which the challenged claims are directed, Dr. Mason's testimony indicates that folic acid already would have been converted to a reduced form by the time pemetrexed is administered, and thus would be available to serve as an antidote to pemetrexed even if Neptune's assertions regarding blockage of DHFR were accurate. Paper 33 at 1-2, 24.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.