

UNITED STATES PATENT AND TRADEMARK OFFICE  
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BEFORE THE PATENT TRIAL AND APPEAL BOARD  
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NEPTUNE GENERICS, LLC,  
APOTEX INC., and APOTEX CORP.,  
Petitioner,

v.

ELI LILLY & COMPANY,  
Patent Owner.

\_\_\_\_\_  
Case No. IPR2016-00237<sup>1</sup>  
Patent No. 7,772,209  
\_\_\_\_\_

**PATENT OWNER'S RESPONSE**

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<sup>1</sup> Case IPR2016-01190 has been joined with the instant proceeding.

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*Eli Lilly & Co. v. Teva Parenteral Medicines, Inc., et al.*, No. 2015-2067 (Fed. Cir.)..... 13

*Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693 (Fed. Cir. 1983)..... 32

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**OTHER AUTHORITIES**

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Neptune's Petition for *inter partes* review sets forth a simple-sounding but fundamentally flawed obviousness case. Neptune's argument—based on Niyikiza I, EP 005, and the '974 patent—is that because homocysteine levels were known to correlate with pemetrexed toxicity, the person of ordinary skill in the art (POSA) would thus be motivated to lower those levels. And, because folic acid and vitamin B<sub>12</sub> were known to lower homocysteine levels, the POSA would thus be motivated to use them to lower homocysteine. Nothing in any of the references that are part of Neptune's ground actually discloses administering vitamin B<sub>12</sub> pretreatment to a cancer patient receiving an antifolate, and the literature taught that vitamin B<sub>12</sub> was *not* relevant to pemetrexed's toxicity. Even setting that basic flaw aside, however, Neptune ignores half the story. And the whole story demonstrates that the claimed invention—a method of administering a life-saving cancer drug that saved the drug from failure during its development—was anything but obvious.

The half of the story that Neptune omits is about pemetrexed's efficacy against cancer. Pemetrexed was the most promising antifolate in decades. And as an antifolate, it works by depriving cells of the folate they need to divide and grow. The folic acid supplementation that Neptune posits would have been so obvious would have been understood by the POSA to act as pemetrexed's antidote. That is, folates and antifolates compete with one another for access to the relevant

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