# United States Court of Appeals for the Federal Circuit

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**NEPTUNE GENERICS, LLC, FRESENIUS KABI USA, LLC,**
*Appellants*

**v.**

**ELI LILLY & COMPANY,**
*Appellee*

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2018-1257, 2018-1258

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Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00237, IPR2016-00240, IPR2016-01190, IPR2016-01191, IPR2016-01335, IPR2016-01337, IPR2016-01341, IPR2016-01343.

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**MYLAN LABORATORIES LIMITED, FRESENIUS KABI USA, LLC,**
*Appellants*

**v.**

**ELI LILLY & COMPANY,**
*Appellee*

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2018-1288, 2018-1290

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Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00318, IPR2016-01340, IPR2016-01393, IPR2016-01429.

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Decided: April 26, 2019

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SARAH ELIZABETH SPIRES, Skiermont Derby LLP, Dallas, TX, argued for all appellants. Appellant Neptune Generics, LLC also represented by PAUL SKIERMONT; MIEKE K. MALMBERG, Los Angeles, CA; JOSHUA HARLAN HARRIS, Neptune Generics, LLC, Chicago, IL.

MICHAEL B. COTTLER, Goodwin Procter LLP, New York, NY, for appellant Fresenius Kabi USA, LLC.

THOMAS J. PARKER, Alston & Bird LLP, New York, NY, for appellant Mylan Laboratories Limited. Also represented by CHARLES ABRAHAM NAGGAR, STEPHEN YANG.

ADAM LAWRENCE PERLMAN, Williams & Connolly LLP, Washington, DC, argued for appellee. Also represented by GALINA I. FOMENKOVA, DOV PHILIP GROSSMAN, DAVID M. KRINSKY, ANDREW P. LEMENS, CHARLES MCCLOUD; JAMES PATRICK LEEDS, Eli Lilly and Company, Indianapolis, IN.

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Before MOORE, WALLACH, and HUGHES, *Circuit Judges*.

MOORE, *Circuit Judge*.

Neptune Generics, LLC, Fresenius Kabi USA, LLC, and Mylan Laboratories Ltd. ("Petitioners") appeal the Patent Trial and Appeals Board's inter partes review ("IPR") decisions holding Petitioners did not establish that claims 1–22 of U.S. Patent No. 7,772,209 are unpatentable for

obviousness. Because the Board did not err in its obviousness analysis, substantial evidence supports its underlying fact findings, and subject matter eligibility is not properly before the court in an appeal from an IPR decision, we affirm.

## BACKGROUND

The '209 patent is owned by Eli Lilly & Co. and relates to administering folic acid and a methylmalonic acid ("MMA") lowering agent, such as vitamin B12, before administering pemetrexed disodium, a chemotherapy agent, in order to reduce the toxic effects of pemetrexed, an antifolate. '209 patent at 1:19–21, 57–61. Antifolates inhibit enzymes used in making the components of DNA and RNA, slowing the ability of cells to divide. *Id.* at 1:36–38. However, antifolates have toxic effects, which can be life threatening. *E.g.*, *id.* at 1:11–12; 1:62–2:4.

The two independent claims in the patent are method of treatment claims. They recite:

> 1. A method for administering pemetrexed disodium to a patient in need thereof comprising administering an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium, wherein
>
> > the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.
>
> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:

> a) administration of between about 350 µg and about 1000 µg of folic acid prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 µg to about 1500 µg of vitamin B12, prior to the first administration of pemetrexed disodium; and
>
> c) administration of pemetrexed disodium.

The Board considered three petitions for IPR, each of which alleged the claims would have been obvious. In IPR2016-00318, Petitioners alleged claims 1–22 would have been obvious over a 1999 article by Hilary Calvert, titled "An Overview of Folate Metabolism: Features Relevant to the Actions and Toxicities of Antifolate Anticancer Agents"; a 1998 abstract by C. Niyikiza, et. al., titled "MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity" ("Niyikiza I"); a 1998 article by John F. Worzalla, et al., titled "Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514"; European Patent Application 0 595 005 A1 ("EP005"); and U.S. Patent No. 5,217,974. In IPR2016-00237, Petitioner alleged the claims would have been obvious over Niyikiza I, the '974 patent, and EP005. In IPR2016-00240, Petitioners alleged the claims would have been obvious over a 1999 article by James J. Rusthoven, et al., titled "Multitargeted Antifolate LY231514 As First-Line Chemotherapy for Patients with Advanced Non-Small-Cell Lung Cancer: A Phase II Study," and EP005.

The Board concluded in each case that the claims were not established to be unpatentable for obviousness. It found that it was known in the prior art that pretreatment with folic acid reduces the toxicity associated with administration of an antifolate, like pemetrexed, but there was not a reason to pretreat with vitamin B12 along with folic

acid before administering pemetrexed to treat cancer. It also found that the skepticism of others, particularly the FDA, supported a conclusion of nonobviousness. Because the Board concluded the independent claims would not have been obvious, it did not consider the additional limitations of the dependent claims.

Petitioners appeal. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

## DISCUSSION

We review the Board's legal determinations de novo and its underlying factual findings for substantial evidence. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). Obviousness is a question of law based on underlying facts. *Id.* Motivation to combine is a question of fact. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016).

On appeal, the parties focus on three references: Niyikiza I, EP005, and another abstract by C. Niyikiza, et al., titled "Relationship of Vitamin Metabolite Profile to Toxicity," ("Niyikiza II"). The lead author on Niyikiza I and II is also the sole named inventor of the '209 patent.

### Pretreatment with Vitamin B12

The Board found that that a skilled artisan would not have been motivated to administer an MMA lowering agent, such as vitamin B12, in addition to folic acid. On appeal, Petitioners argue that in making this finding, the Board did not consider EP005 for all that it teaches. Specifically, Petitioners point to EP005's disclosure of the administration of folic acid and vitamin B12 to lower homocysteine levels for all purposes. We disagree and hold that substantial evidence supports the Board's findings.

The Board's findings are based on the prior art's disclosure of the relationships between various biochemicals and toxicity. The Board found that deficiencies in both vitamin

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