UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE (I-MAK), INC.
Petitioner

v.

GILEAD PHARMASSET LLC
Patent Owner

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Case No. IPR2018-00125
U.S. Patent No. 8,633,309

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PETITIONER'S REQUEST FOR REHEARING

I. INTRODUCTION

Petitioner Initiative for Medicines, Access & Knowledge (I-MAK), Inc. ("Petitioner") respectfully requests rehearing of the Board's Decision Denying Institution of *Inter Partes* Review ("IPR") of Gilead Pharmasset LLC's ("Gilead") U.S. Patent 8,633,309 ("the '309 patent") ("Decision"; Paper 9) regarding the asserted ground of obviousness over Sofia '634 and Congiatu, because Congiatu and Dr. Fortunak's declaration are substantial evidence that is not cumulative of the evidence of record during prosecution and that in fact overcomes the Examiner's express reason for allowance that the claimed compound was unexpectedly more potent. There is no evidence of record to support the Examiner's finding, and Petitioner's new additional evidence directly rebuts it.

II. LEGAL STANDARD

A party may request rehearing of a denial of institution by, "identify[ing] all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d). The Board reviews its decision for "abuse of discretion," *Id*. at § 42.71(c), which includes basing the decision on, "an erroneous conclusion of law or clearly erroneous factual finding." *PPG Indus., Inc. v. Celanese Polymer Specialties Co.*, 840 F.2d 1565, 1567 (Fed. Cir. 1988).

III. CONGIATU AND DR. FORTUNAK'S DECLARATION ARE NOT CUMULATIVE TO THE EVIDENCE OF RECORD DURING PROSECUTION, AND INDEED DIRECTLY REBUT THE EXAMINER'S UNSUPPORTED SOLE REASON FOR ALLOWANCE

In denying institution of asserted Ground 2, the Board stated in the Decision that, "Petitioner [] relies on Congiatu for teachings that are substantially the same as Sofia '634, such that the alleged teachings of Congiatu are cumulative to the alleged teachings of Sofia '634." Paper 9, 17. However, the Board overlooked several of Congiatu's teachings that are not present in Sofia '634 and are thus materially additive over the evidence that was of record during prosecution.

First, Congiatu taught the correct stereochemical assignments of phosphorous diastereomers, which is lacking in Sofia '634. Ex. 1006, 3. Sofia '634 teaches separating the diastereomers and testing them separately. It does not teach the assignment of which diastereomer is R- or S-. Ex. 1005, 694 ("The absolute stereochemistry of the P-chiral center of the diastereomers were not determined.") The Table cites the diastereomers as "fast moving" and "slow moving" by chromatography without stereochemical assignment. *Id*.

Second, Congiatu cited the previous work of Saboulard (1999) and Siccardi (2004) that taught why a POSA would expect differences in activity between different phosphorous diastereomers. Ex. 1006, 2. While Sofia '634 taught diastereomers may have substantially different antiviral activity, Paper 9, 17 (citing arguments made in the Petition), Congiatu provided additional teaching that the

difference in activity was not only possible, but would be expected. This is substantially more than what was taught by Sofia '634.

Third, Congiatu actually found that an Sp diastereomer was more active than an Rp diastereomer, just like the nucleoside phosphoramidates claimed in the '309 patent. Ex. 1006, 3. The Sofia evidence of record during prosecution did not show that the Sp diastereomer was more potent, only that one diastereomer at Phosphorous could be more potent than the other, without an assignment or understanding of which diastereomer was more potent. Ex. 1005, 694. Thus, Congiatu provides additional evidence above and beyond Sofia '634 that such result was not unexpected.

Fourth, Congiatu taught that a POSA would look to the specific disease state or tissues of interest in assessing the potential of phosphoramidate prodrugs. Ex. 1006, 2. Thus, Congiatu taught that "Nucleoside analogues represent an extremely effective tool for the treatment of cancer and viral infections." *Id.*, 1. Congiatu further taught (as Sofia '634 does not) that phosphoramidate prodrugs of nucleoside analogues were widely used (by their research group and others) to overcome general limitations of nucleoside analogues. Congiatu discloses the general knowledge (additive to Sofia) that phosphoramidates were used to: 1) improve lipophilicity and cell penetration; and 2) bypass the limitations of intracellular activation of nucleoside analogues by kinases. *Id.* Congiatu discloses

(as Sofia '634 does not) that this approach had been advanced into human treatment. *Id.*, 2. Congiatu also taught (as Sofia '634 does not) that phosphoramidates are activated intracellularly by the action of esterases and phosphoramidases and, thus, a POSA would expect a ProTide prodrug to have an activity pattern that is heavily dependent upon the target tissue, and not so much by the particular nucleoside structure. *Id.*

Further, Congiatu cites to, and explains (as Sofia '634 does not) the findings of Saboulard (1999) and Siccardi (2004), e.g., that Saboulard found that hydrolysis of the carboxyl ester group "…is a fundamental step for the activation of phosphoramidates." *Id.* Congiatu also taught that Siccardi's teaching: "Enzymatic stability in the extracellular environment and in different cellular preparations was found to be stereospecific with large and unpredictable differences in stereoselective metabolic rate noted by Siccardi et al." *Id.* This teaching in Congiatu reveals the motivation of a POSA to separate the phosphoramidate diastereomers of such nucleosides prodrugs. It also reveals why a POSA would not find it unexpected that these diastereomers might have large differences in activity.

Accordingly, Congiatu teaches the separation of phosphoramidate diastereomers (at phosphorous) by chromatography. Congiatu also reveals a substantial difference in activity between the more-active Sp diastereomer and the less-active Rp diastereomer. *Id.*, 2-3.This is again more than what Sofia '634

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