Paper No. ___
Filed: January 8, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARAMACEUTICALS INC.,
Petitioner,

v.

ASTRAZENECA AB,
Patent Owner.

Case IPR2015-01340
Patent RE44,186

PETITIONER MYLAN PHARMACEUTICALS INC.'S REQUEST FOR REHEARING PURSUANT TO 37 C.F.R. §42.71

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BASIS FOR REHEARING 1

A. Legal Standards 1

B. Erroneous Interpretation of Law 2

C. Factual Findings Not Supported by Substantial Evidence 5

III. PANEL COMPOSITION 12

IV. CONCLUSION 13

I. INTRODUCTION

In response to the Decision Denying Institution of *Inter Partes* Review entered December 9, 2015, (Paper 12, hereinafter "Decision") and pursuant to 37 C.F.R. § 42.71(d), Mylan Pharmaceuticals Inc. ("Petitioner") hereby respectfully requests the Patent Trial and Appeal Board ("Board") reconsider its decision denying institution for *inter partes* review of U.S. Patent No. RE44,186 E ("the '186 patent").

II. BASIS FOR REHEARING

A. Legal Standards

Pursuant to 37 C.F.R. § 42.71(d), a party may request rehearing of a decision by the Board whether to institute a trial. "The request must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, opposition, or reply." *Id.* The Board will review the previous decision for an abuse of discretion. 37 C.F.R. § 42.71(c). "An abuse of discretion may be indicated if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors." IPR 2013-00369, Paper 39 at 2-3 (citing *Star Fruits S.N.C. v. United States*, 393 F.3d 1277, 1281 (Fed. Cir. 2005)).

The Petition asserted in Ground 1 that a combination of Ashworth I, Villhauer I, Raag and Hanessian rendered obvious the compound of claim 25 of the '186 patent, and this compound was encompassed by each of the other

challenged claims. Decision, p. 5. According to the '186 patent, the compound of claim 25 (referred to for convenience in the Petition as saxagliptin) was said to be an inhibitor of the enzyme dipeptidyl peptidase IV (DP-IV) and therefore useful to ameliorate the diabetic condition. *Id.*, p. 3.

The Decision states that, "we accept Petitioner's assertion that a person[] of ordinary skill would have chosen compound 25 as a lead compound . . . [and] focus on whether the evidence of record supports Petitioner's contention that one of ordinary skill in the art would have been motivated to replace the 6-carbon cyclohexyl group at the 2-position of compound 25 with a 10-carbon adamantyl moiety." Dec., pp. 7-8.

B. Erroneous Interpretation of Law

The Decision first found that there was insufficient motivation for one of ordinary skill to increase the stability of compound **25** by substituting a larger cycloalkane—in particular adamantyl—for the cyclohexyl group of compound **25**. The Decision concludes that Villhauer I, Ex. 1008, which discloses the adamantyl, "fails to cure the lack of rationale for substituting adamantyl at the 2-position of compound 25." Dec., p. 11. The Decision bases its conclusion on the following statement, which contradicts the substantial evidence and errs as a matter of law: "[A]lthough Villhauer I identifies adamantyl as a possible moiety in '[e]ven more preferred compounds,' ***adamantyl groups are conspicuously absent from the preferred examples of Villhauer [I]***—'Examples 1, 3, 5, 8, and 12 [, which] are

the preferred agents of the invention.' Ex. 1008, 5, 21; *see* Pet. 26" (Dec., p. 11, emphasis added).

An obviousness analysis under § 103 does not require that a prior art reference, such as Villhauer I, identify a compound as a most preferred or exemplified agent of the invention. *Merck & Co. v. Biocraft Labs., Inc.,* 874 F.2d 804, 807 (Fed. Cir. 1989). "In a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" (*Merck*, quoting *In re Lamberti,* 545 F.2d 747, 750 (C.C.P.A. 1976)); *see also Boston Sci. Scimed, Inc. v. Cordis Corp.,* 554 F.3d 982, 991 (Fed. Cir. 2009) (citing *Merck* in holding that a prior art reference containing two separate embodiments that when combined taught the claimed invention, "need not have recognized the additional benefit of one embodiment to have rendered the claim obvious").

Thus, it was legal error for the Board to observe as particularly noteworthy in its obviousness analysis that adamantyl groups were "conspicuously absent from the preferred examples of Villhauer [I]." Dec., p. 11. Not only does Villhauer I expressly state that an adamantylated compound is an "even more preferred compound of the invention," but, in addition and contrary to the statement in the Decision, three different examples of adamantylated compounds are identified in Villhauer I, see Examples 47, 49 and 53 (Ex. 1008, p. 13) (see Pet., p. 9, pointing to the synthesis and characterization of an adamantyl-containing compound, Example 47, in Villhauer I). Patent Owner's evidence corroborates Petitioner's

evidence: Villhauer (Novartis) was pursuing its own patent to DP-IV inhibitor compounds containing the very same adamantyl groups. *See*, U.S. Patent No. 6,166,063 (Ex. 2013; "Villhauer II"), Abstr. ("wherein R is substituted adamantyl"); col. 2, ll. 20-35 (depicting compounds of formula Ia and Ib), and elsewhere throughout the patent disclosure. Villhauer II has a priority date of Dec. 10, 1998, well prior to the March 10, 2000, priority date of the '186 patent. Villhauer II further discloses an adamantyl group that is hydroxylated in exactly the same position as saxagliptin. Ex. 2013, Example 1, p. 5. Thus, again, Petitioner and Patent Owner provided substantial evidence *supporting* Ground 1 of the Petition. Simply put, the Board's decision not only lacks substantial evidence, it contradicts the substantial evidence of record. The prior art indisputably discloses adamantylated (and hydroxylated adamantyl) DP-IV inhibitors.

When Villhauer I is correctly interpreted and accorded appropriate weight in a legally correct obviousness analysis, the requisite teaching and rationale for substituting adamantyl at the 2-position of compound **25** of Ashworth I are clearly provided. It was legal error for the Board to base its Decision on what it perceived to be the "conspicuous[] absen[ce]" (Dec., p. 11) of a preferred Example of an adamantylated compound in Villhauer I, and to draw inferences adverse to a conclusion of obviousness.

C. Factual Findings Not Supported by Substantial Evidence

As noted in the Decision, the Petition identifies a rationale to substitute the cyclohexyl group of Ashworth I with the even larger adamantyl group of Villhauer I. Dec., p. 8. Adamantyl is, after all, simply an enlarged version of cyclohexyl: effectively four interconnected cyclohexyls, in which each cyclohexyl shares two bonds with each of the other three. Depicted in Pet., p. 8. Further, Villhauer uses it in their own DP-IV inhibitors, as discussed above. Ex. 1008; Ex. 2013. But the Decision, reading Ashworth I in view of Ashworth II (Ex. 2001), concludes that together they do not support a motivation to increase the stability of lead compound **25**. Dec., p. 8. When Ashworth II is correctly considered, however, particularly in the context of Ashworth I's teachings, the Board's factual findings are contradicted by substantial evidence. As explained below, Ashworth I and II's teachings provide ample rationale for substitution of a larger group, one already used with DP-IV inhibitors (i.e., adamantyl) for the cyclohexyl group of compound **25**. This request is Petitioner's first opportunity to address this aspect of Ashworth II and is thus timely.

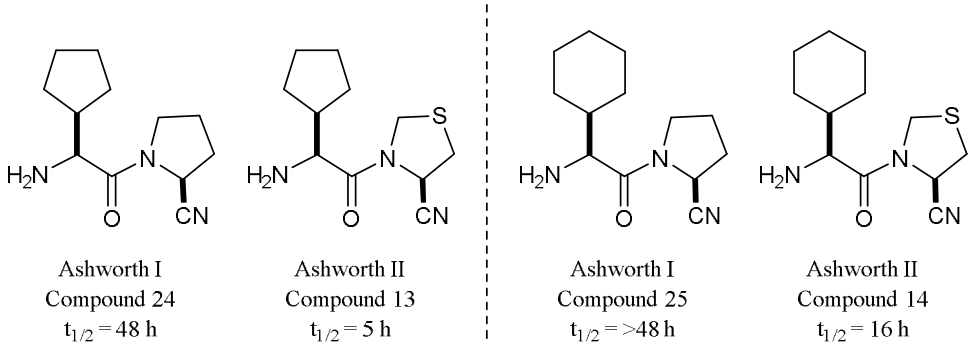
The Decision finds compound **25** is stable in its original form, and finds no motivation to further modify it to increase its stability. Dec., p. 10. This finding is based on long-overturned law and less than a scintilla of probative evidence: that the Ashworth II publication focused on increasing potency, not stability ("Not surprisingly, the resulting publication, Ashworth II, [footnote omitted] was not directed to increasing stability, but 'to improv[ing] the potency of this class of

inhibitors.' Ex. 2001, 2746 [. . .] Ashworth II, therefore, further suggests that compound **25** is stable in its original form"). Dec., p. 10. The absence of a suggestion to further improve stability in a single paper is not evidence that the authors of the paper rejected the possibility of further stability optimization. There is no evidence to support such an inference. In effect, the Decision's finding erroneously requires Ashworth II to provide the motivation for modifying Ashworth I. Long before even *KSR*, the Federal Circuit rejected any requirement that the prior art must suggest its own modification. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc).

In any case, the Decision's factual findings regarding Ashworth II (Ex. 2001) and its purported affirmance of the stability of compound **25** in Ashworth I (Ex. 1007) are incorrect in several aspects and lack substantial evidence. If anything, as explained below, Ashworth II highlights the potential ***instability*** of compound **25** when making changes to the pyrrolidine ring portion of the molecule (e.g., to improve potency) and motivates further improvement to the stability of compound **25** of the kind established in the Petition.

Once again, the Patent Owner's evidence actually supports the Petition: compounds **13** and **14** of Ashworth II (Ex. 2001, p. 2748, Table II) are ***identical to compounds 24 and 25 of Ashworth I, but for the inclusion of sulfur in the pyrrolidine ring***. Compare compound **13** (cyclopentylglycine in the Xaa position; Table II of Ashworth II, p. 2748) with compound **24** (cyclopentylglycine in the Xaa position; Table II of Ashworth I, p. 1166); and compare compound **14**

(cyclohexylglycine in the Xaa position; Table II of Ashworth II, p. 2748) with compound **25** (cyclohexylglycine in the Xaa position; Table II of Ashworth I, p. 1166). The structures are set forth below for ease of comparison:



Comparing the stability of compound **25** with compound **14** of Ashworth II, it can be seen that the half-life, $t_{1/2}$, falls dramatically with modification of the pyrrolidine ring: from >48 hours for compound **25**, to 16 hours for compound **14**. The same holds true for compound **24**; when the pyrrolidine ring is modified, creating compound **13**, the $t_{1/2}$ falls from 48 hours to 5 hours.

Thus, Ashworth II's attempt to increase the DP-IV inhibition potency of Ashworth I compounds **24** and **25**, by modifying the pyrrolidine ring to include a sulfur, dramatically decreases the stability of the compounds. The statement in the Decision that "Ashworth II, therefore, further suggests that compound 25 is stable in its original form" (Dec., p. 10) overlooks the very significant fact that the attempt in Ashworth II to improve potency of compound **25** substantially diminished the stability of the compound. In view of the teachings of Ashworth II, one of ordinary skill would have been highly motivated to improve the stability of compound **25** while improving potency. It is worth noting that the Decision did not reach evidence in the Petition that it would have been obvious to improve the

potency of compound **25** by modifying the pyrrolidine ring, as was done by both Ashworth I and Villhauer I, by adding cyclopropyl (as taught by Hanessian), which was added in the same place as the sulfur as disclosed in Ashworth II.

Apart from Ashworth II's support for increasing the stability of lead compound **25**, factual errors are made in the Decision regarding Ashworth I. These errors lead to a lack of substantial evidence for the Decision's conclusion that a person of ordinary skill would not have been motivated to substitute a larger cycloalkyl moiety, i.e., adamantyl, for the cyclohexyl group of compound **25**. Dec., p. 12.

As noted above, the Decision determines that Villhauer I, "fails to cure the lack of rationale for substituting adamantyl at the 2-position of compound 25." (Dec., p. 11) This conclusion contradicts the substantial evidence of record and errs as a matter of law. For example, Lin states, "[DP-IV] substrates **require the presence of a . . . free N-terminus**." Pet., p. 19, citing Ex. 1015, p. 14020 (emphasis added). Ashworth I further states, "[N-terminal] α-amino acid derivatives were the most potent compounds." Pet., p. 25, citing Ex. 1007, p. 1165. Had the Board properly considered the teachings of Villhauer I in the context of the art as a whole, i.e., Lin and Ashworth I, it would have found direct motivation to substitute the adamantyl moiety at the 2-position of compound **25**.

At page 13, the Decision notes the express statement in Ashworth I that "as can be seen in Table I, lipophilic amino acids gave more potent compounds." But the Decision finds two exceptions in the many compounds shown in Table 1, such

that it concludes that Ashworth I's express statement "does not invariably hold." Dec., p. 13. First, the general trend does not have to invariably hold to provide a clear and direct teaching. Second, compound **9** (substituted with valine) being more potent than compound **11** (substituted with *tert*-butyl) is identified as an exception because valine "contains less 'beta-branching.'" Dec., p. 13. However, Ashworth I simply identifies that β-branched derivatives were the most potent compounds. Ashworth I does not suggest that *more* β-branching produces *even more* potent compounds. Thus, this alleged exception is the result of a misconstruction of Ashworth's teachings and lacks substantial evidence in support. The actual trend, that large, β-branched and more lipophilic amino acids provide more potent compounds, is clearly taught by Ashworth I to apply to Table II: "[w]e then applied these findings [from Table I] to a series of 2-cyanopyrrolidides [of Table II] . . . The [Structure-Activity Relationship] for the N-terminal residue developed in the pyrrolidide series [of Table I] **correlated well** for the dipeptide nitrile series [of Table II]." Ex. 1007, p. 1165 (bold added); Pet., p. 26. The Decision (p. 13), however, considered the compounds of Table I less pertinent to the analysis than compounds **24** and **25** found in Table II, when its teachings were actually supportive of Table II.

Accepting only for the purpose of this Rehearing Request the Board's Decision that Table I of Ashworth I is less pertinent, the findings regarding Table II of Ashworth I, particularly compounds **24** and **25**, are factually incorrect. The Decision states, "[A]s Patent Owner points out, Ashworth I compounds 24-27

exhibit comparable stabilities with half-lives of at least 48 hours despite having substituents of varying size and composition in the 2-position." Dec., pp. 10-11. This assessment is incorrect. The cyclohexylated (Chg) compound **25** is more stable than the smaller, cyclopentylated compound **24** (i.e., a half-life of >48 hours, versus precisely 48 hours). The extent to which it is more stable is unknown based on the data presented in Ashworth I, as the data simply show compound **25** as having a longer half-life, i.e., >48 hours, and thus being more stable than compound **24**.

This is also the case for compound **27**, containing *tert*-butyl glycine (Tbg). The *tert*-butyl substituent of compound **27** is bulkier than the isoleucine of compound **26**, having one more degree of beta-branching than isoleucine. That compound **27** is more stable than compounds **24** and **26** is consistent with its increased bulk and lipophilicity, as taught by Ashworth I. But again, the degree to which compound **27** is more stable than compounds **24**, **26**, or even perhaps **25**, is unknown. There is, however, a clear trend apparent from Table II of Ashworth I: larger, more lipophilic substituents at the 2-position yield more stable compounds. The extent to which stability is enhanced is not assessed, but nonetheless the trend is readily apparent.

The Decision further incorrectly asserts that isoleucine (found in compound **26**) is less bulky than cyclopentane, when there is no data to support this factual finding. Dec., p. 11. Cyclopentane (Chg) and isoleucine (Ile) are comparable in terms of steric bulk and lipophilicity; while cyclopentane has one more methylene

unit and isoleucine has more freely rotatable bonds and thus is comparable to cyclopentane. That compounds **24** and **26** have the same stability (i.e., half-lives of 48 hours) in Table II is consistent with their similar three-dimensional shapes, and does not negate the clear trend of Table II, that larger, more lipophilic substituents yield more stable compounds.

Thus, the Decision's factual determination that "Ashworth I compounds 24-27 exhibit comparable stabilities" (Dec., p. 10) is incorrect; only the stability of compound **24** and **26** are comparable. The stability of compound **25** and **27** are reported only as something greater than 48 hours, and thus indeterminate.

In incorrectly analyzing the data of Ashworth I (and Ashworth II, as discussed above), the Decision's conclusions contradict the substantial evidence. Ashworth I teaches a strong and clear trend: larger substituents at the α-position of the N-terminal amino acid residue of DP-IV inhibitor compounds result in heightened stability. Ashworth II teaches that perturbations to the pyrrolidine decrease stability. This trend leads those in the art to adamantyl as a bulkier version of the cyclohexyl in compound **25**. Villhauer I expressly recites adamantyl is an "even more preferred" substituent on the N-terminus of DP-IV inhibitors. The Decision's erroneous interpretation of law regarding Villhauer I were combined with key factual findings in Ashworth I and II that are not supported by substantial evidence. When corrected, the combination of art leads to compound **25** of Ashworth I having a substituted adamantyl group at the precise position found in saxagliptin, the compound of claim 25 of the '186 patent.

III. PANEL COMPOSITION

A new panel may be appropriate to consider this rehearing request and, should the Board determine to institute trial, to conduct the trial. Petitioner learned after the entry of the Decision that the authoring administrative patent judge was a partner at opposing counsel's law firm as of June 2014. [1] When the Petition was filed, Petitioner identified a related lawsuit filed on June 2, 2014 for AstraZeneca against Mylan for infringement of the '186 patent. Pet., p. 16, citing *AstraZeneca AB v. Mylan Pharmaceuticals Inc.*, 14-cv-00696 (DED 2014). Counsel for AstraZeneca in the District Court litigation against Mylan is also lead counsel for AstraZeneca in this proceeding. The administrative patent judge who was a partner at opposing counsel's firm in June 2014 had also appeared as co-counsel with AstraZeneca's lead counsel in several other lawsuits against generic drug companies. *E.g.*, *Cephalon, Inc. v. Apotex Corp.*, 10-cv-01078 (DED) & 10-cv-22997 (FLSD); *Astellas US LLC et al. v. Nycomed U.S. Inc.*, 10-cv-08274 (NYSD) & 10-cv-05599 (NJD).

Petitioner does not suggest there was an actual impropriety: the mere appearance of possible impropriety is sufficient to justify reconsideration by a

[1] See LinkedIn page listing employment at Finnegan in June 2014. June 2 was the first weekday of the month.

newly composed panel.[2] *Aetna Life Ins. Co. v. Lavoie*, 475 U.S. 813, 825 (1986) (explaining actual bias is not required); *Caperton v. AT Massey Coal Co., Inc.*, 129 S. Ct. 2252, 2264 (2009) (same). Petitioner is raising the issue at its first opportunity after discovery. *Lavoie*, 475 U.S. at 817-19 (holding timely challenge first raised after request for reconsideration filed); see also *Liljeberg v. Health Servs. Acquisition Corp.*, 486 U.S. 847, 868-69 (1988).

Petitioner respectfully suggests rehearing by a newly composed panel.

IV. CONCLUSION

The Decision erred as a matter of law in relying on a finding that adamantyl groups were "conspicuously absent" from the preferred examples of a prior art reference, Villhauer I (Ex. 1008), contradicting precedent holding that a modification need not even be preferred. The Decision's finding that Villhauer I lacked examples of adamantyl-containing compounds was also lacking in substantial evidence: the Petition also noted that Villhauer provided the compound of Example 47, an adamantyl-containing DP-IV inhibitor. Pet., p. 9.

In addition, in assessing the impact of Ashworth II (Ex. 2001), the Decision lacks substantial evidence for concluding that Ashworth II discourages further improvements to the stability of lead compound **25** identified in Ashworth I (Ex.

[2] See, e.g., 28 U.S.C. 455(b)(2) (barring participation of a district court judge where former firm worked on matter in controversy while judge was still there).

1007). In fact, Ashworth II shows that small perturbations to the pyrrolidine ring of compound **25** can significantly diminish the stability of the compound, which would have motivated offsetting improvements to compound stability. A person of ordinary skill in the art would have found it obvious to modify compound **25** by replacing the cyclohexyl group with an even larger interconnected cyclohexyl group, adamantyl, as described in Villhauer I.

Petitioner respectfully suggests rehearing by a newly composed panel and requests institution of trial.

Respectfully submitted,

Dated: January 8, 2016

/ Steven W. Parmelee /
Steven W. Parmelee
Reg. No. 31,990
Rick Torczon
Reg. No. 34,448

CERTIFICATE OF SERVICE

This is to certify that I caused to be served a true and correct copy of the foregoing Petitioner Mylan Pharmaceuticals Inc.'s Request for Rehearing, on this 8th day of January, 2016, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Charles E. Lipsey
Finnegan, Henderson, Farabow,
Garret & Dunner, L.L.P.
11955 Freedom Drive
Reston, VA 20190
Tel: 571-203-2700
Fax: 202-208-4400
Email: charles.lipsey@finnegan.com

M. David Weingarten
Finnegan, Henderson, Farabow,
Garret & Dunner, L.L.P.
3500 SunTrust Plaza
303Peachtree Street, N.E.
Atlanta, GA 3038
Tel: 404-653-6400
Fax: 404-653-6444
Email:
david.weingarten@finnegan.com

Eric E. Grondahl
McCarter & English LLP
City Place I
185 Asylum St.
Hartford, CT
Tel: 860-275-6704
Fax: 860-724-3397
Email: egrondahl@mccarter.com

Respectfully submitted,

Dated: January 8, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990