IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
Petitioner,

v.

MERCK SHARP & DOHME CORP.
Patent Owner.

U.S. Patent No. 7,326,708 to Cypes et al.
Issue Date: February 5, 2008
Title: Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor

Inter Partes Review No.: IPR2020-00040

Petition for *Inter Partes* Review of U.S. Patent No. 7,326,708
Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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1004	WO 03/004498 to Edmonson
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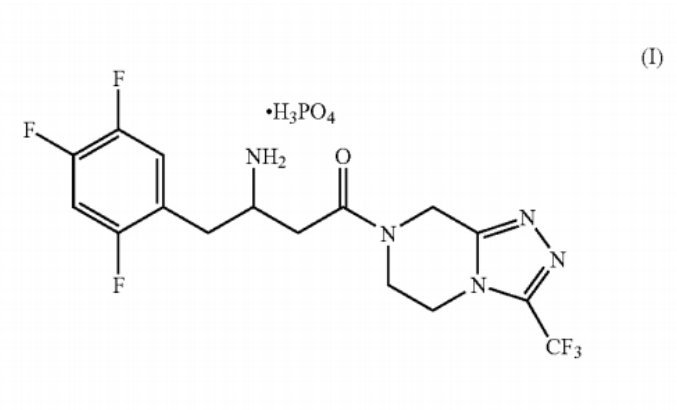
I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *Inter Partes* Review ("IPR") seeking cancellation of Claims 1-4, 17, 19, and 21-23 ("challenged claims") of U.S. Patent No. 7,326,708 ("the '708 patent") (EX1001), which is assigned to Merck, Sharpe & Dohme Corp. ("Merck" or "Patent Owner").

II. OVERVIEW

The '708 patent claims a compound commonly known as sitagliptin phosphate (depicted below), or a hydrate thereof. EX1001, Claim 1 at 16:1-14.[1]



[1] Sitagliptin is also known as 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine or 7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-l,2,4-triazolo[4,3-a]pyrazine. EX1004, 15:64-66, Example 7; EX1002, ¶65.

Dependent claims 2-3, 17, 19, and 21-23 recite the phosphate salt of sitagliptin while Claims 4-16, 18, 20, and 24 recite the monohydrate thereof or various monohydrate forms thereof. EX1001, 15:63-18:36. The '708 patent, however, is not the first disclosure of sitagliptin phosphate. WO 03/004498 ("WO '498") (EX1004), prior art to the '708 patent under 35 U.S.C. § 102(a), discloses sitagliptin and its "pharmaceutically acceptable salts." Patent Owner can hardly dispute otherwise since the '708 patent plainly admits these facts in the "Background of the Invention":

> WO 03/004498 (published 16 Jan. 2003), assigned to Merck & Co., describes a class of beta-amino tetrahydrotriazolo [4,3-a]pyrazines, which are potent inhibitors of DP IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is **4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine**. **Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of WO 03/004498.**

EX1001, 1:49-57 (emphasis added). "Admissions in the specification regarding the prior art are binding on the patentee." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988) ("A statement in the patent that something is in the prior art is binding on the applicant and patentee for

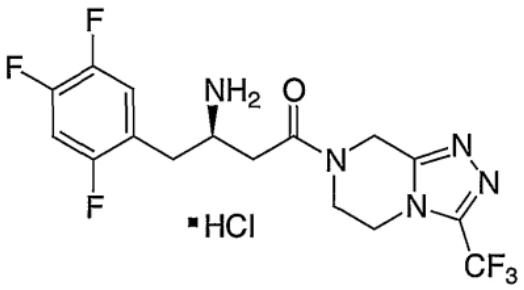
determinations of anticipation and obviousness."); *Sjolund v. Musland*, 847 F.2d 1573, 1577-79 (Fed. Cir. 1988) (patent specification admitted that certain matter was prior art, and thus "the jury was not free to disregard [that matter]" and "must have accepted [it] as prior art, as a matter of law"); *One World Technologies Inc. v. The Chamberlain Group Inc*., IPR2017-00126, Paper 67 at 14-15 (P.T.A.B. Apr. 4, 2019) ("[T]he Court of Customs and Patent Appeals [has] long held that admissions in a patent may be considered prior art for any purpose.").[2]

As to "pharmaceutically acceptable salts," WO '498 teaches the term can refer to salts generated from either bases or acids. EX1004, 9:27-30. As to the acid salts, "[p]articularly preferred" are "citric, hydrobromic, hydrochloric, maleic, **phosphoric**, sulfuric, fumaric, and tartaric acids." *Id*., 10:14-15 (emphasis added). And much like the '708 patent, the compounds of WO '498 are dipeptidyl peptidase-IV enzyme inhibitors that are useful for the treatment or prevention of diseases such as diabetes and particularly type 2 diabetes. EX1004, Abstract.

[2] The fact that the patentee's admissions about WO '498 were made in the "Background of the Invention" of the '708 patent gives further weight to this prior art admission. *One World Technologies Inc*., IPR2017-00126, Paper 67 at 15.

As to salts of sitagliptin specifically, WO '498 exemplifies one of the "[p]articularly preferred" salts (i.e., the hydrochloride salt) of sitagliptin as Example 7:

EXAMPLE 7



Id. at 46:1-4. There is no dispute about this fact either; the '708 patent admits it. EX1001, 4:19-22. Further, WO '498 claims sitagliptin and its "pharmaceutically acceptable salts." EX1004, Claim 15 (7th structure), 55 (bottom structure); *id*., 60:5 ("pharmaceutically acceptable salts thereof").

In reference to WO '498, the '708 patent inventors may state: "there is no specific disclosure in the above reference of the newly discovered monobasic dihydrogen phosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine." EX1001, 1:58-62. However, WO '498 teaches *and claims* sitagliptin and its "pharmaceutically acceptable salts" and then identifies the phosphoric acid salt as a "[p]articularly preferred" salt. *Id*., 10:14-15. Under applicable legal precedents,

sitagliptin phosphate was disclosed. For that matter, any attempt by Patent Owner to devalue the disclosure of WO '498 and assert that it does not teach sitagliptin phosphate is belied by the fact that U.S. 6,699,871 (EX1007), which is related to WO '498, is listed in the FDA Orange Book *along with* the '708 patent for Janumet® and Januvia®. EX1008 & EX1009.[3]

III. STANDING (37 C.F.R. § 42.104(A)); PROCEDURAL STATEMENTS

Petitioner certifies that: (1) the '708 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '708 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith are a Power of Attorney and an Exhibit List pursuant to Section 42.10(b) and Section 42.63(e), respectively. The required fee is paid when filing the Petition and the Office is authorized to charge any fee

[3] WO '498 (EX1004) and U.S. 6,699,871 (EX1007) both claim priority to U.S. Provisional Application No. 60/303,474 and share the same specification in all relevant material respects. *Compare* EX1004, 9:27-10:15 ("pharmaceutically acceptable salts"), 46:1-5 (Example 7, sitagliptin hydrochloride) *with* EX1007, 6:38-7:4 ("pharmaceutically acceptable salts"), 32:1-16 (Example 7, sitagliptin hydrochloride). WO '498 was not used by the Examiner during prosecution of the '708 patent to formulate any prior art rejection.

deficiencies and credit overpayments to Deposit Acct. No. DA501290 (Customer ID No. 27160).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

A. Each Real Party in Interest (37 C.F.R. § 42.8(b)(1))

The following real parties in interest are identified: Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan N.V.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters Involving the '708 Patent

The '708 patent is currently the subject of the following litigations: *Merck Sharp & Dohme Corp. v. Mylan Pharmaceuticals Inc. et al.*, 1:19-cv-00101 (N.D. W. Va.); *Merck Sharp & Dohme Corp. v. Mylan Pharmaceuticals Inc. et al.*, 1:19-cv-01489 (D. Del.); *Merck Sharp & Dohme Corp. v. Alvogen Pine Brook f/k/a Alvogen Pine Brook, Inc. et al.*, 1:19-cv-00310 (D. Del.); *Merck Sharp & Dohme Corp. v. Anchen Pharmaceuticals, Inc. et al.*, 1:19-cv-00311 (D. Del.); *Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, 1:19-cv-00312 (D. Del.); *Merck Sharp & Dohme Corp. v. Apotex Inc. et al.*, 1:19-cv-00313 (D. Del.); *Merck Sharp & Dohme Corp. v. Zydus Pharmaceuticals (USA) Inc. et al.*, 1:19-cv-00314 (D. Del.); *Merck Sharp & Dohme Corp. v. Macleods Pharmaceuticals, Ltd. et al.*, 1:19-cv-00316 (D. Del.); *Merck Sharp & Dohme Corp. v. Watson Pharmaceuticals, Inc. et al.*, 1:19-cv-00317 (D. Del.); *Merck Sharp & Dohme Corp. v. Teva Pharmaceuticals USA, Inc.*,

1:19-cv-00318 (D. Del.); *Merck Sharp & Dohme Corp. v. Sun Pharma Global FZE et al.*, 1:19-cv-00319 (D. Del.); *Merck Sharp & Dohme Corp. v. Torrent Pharmaceuticals Limited et al.*, 1:19-cv-00320 (D. Del.); *Merck Sharp & Dohme Corp. v. Wockhardt Bio AG et al.*, 1:19-cv-00321 (D. Del.); *Merck Sharp & Dohme Corp. v. Lupin Ltd. et al.*, 1:19-cv-00347 (D. Del.); *Merck Sharp & Dohme Corp. v. Torrent Pharmaceuticals Limited et al.*, 1:19-cv-00872 (D. Del.); and *In re Sitagliptin Phosphate ('708 & '921) Patent Litigation*, C.A. No. 19-md-2902-RGA (D. Del.).

2. Administrative Matters

The Public Patent Application Information Retrieval (PAIR) website indicates that there are no related United States patents or pending applications.

C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4))

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V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(A))

Petitioner requests IPR and cancellation of Claims 1-4, 17, 19, and 21-23 of the '708 patent. Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '708 PATENT

The '708 patent, entitled "Phosphoric acid salt of a dipeptidyl peptidase-IV inhibitor," issued on February 5, 2008, from U.S. Appl. No. 10/874,992 ("the '992 application"), and ultimately claims a benefit of priority from U.S. Provisional Application No. 60/482,161 filed June 24, 2003.[4] EX1001. The '708 patent issued

[4] Petitioner notes that in the related district court litigation, Patent Owner has recently contended that the priority date for Claims 1 and 2 of the '708 patent is no later than December 13, 2001, i.e., earlier than June 24, 2003. EX1015, Response to Interrogatory No. 1.

with 24 claims, although the instant petition only seeks to challenge Claims 1-4, 17, 19, and 21-23.

The '708 patent is allegedly directed to "dihydrogenphosphate salt of 4-oxo-4-3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine [which] is a potent inhibitor of dipeptidyl peptidase-IV and is useful for the prevention and/or treatment of non-insulin dependent diabetes mellitus, also referred to as type 2 diabetes." EX1001, Abstract. According to the '708 patent, "[i]nhibition of dipeptidyl peptidase-IV (DP-IV), an enzyme that inactivates both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), represents a novel approach to the treatment and prevention of Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM)." EX1001, 1:31-37.

At a high level, Claims 1-4 are directed to sitagliptin phosphate "or a hydrate thereof," sitagliptin phosphate in the (R) or (S) configuration, or a crystalline monohydrate of (R)-sitagliptin phosphate. Claim 17 is directed to a pharmaceutical composition containing (R)-sitagliptin phosphate. Claim 19 is directed to a method for the treatment of type 2 diabetes using (R)-sitagliptin phosphate. Claims 21-23 depend ultimately from Claim 2. Claims 21 and 22 are process claims and Claim 23 is a product-by-process claim for making (R)-sitagliptin phosphate.

Turning to the examination of the ’708 patent, a complete copy of the prosecution history of the ’708 patent is attached as EX1010. The Examiner never asserted any prior art rejection for any of the allowed claims under 35 U.S.C. § 102 or § 103. Furthermore, no declaration or other evidence of unexpected results or any other secondary considerations were presented to the Examiner.

VII. CLAIM CONSTRUCTION

Under applicable guidance, the claims must be given “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *See* 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). Petitioner is unaware of any prior claim construction determination concerning the ’708 patent in a civil action or a proceeding before the International Trade Commission. To the extent the ’708 patent specification defines any term, Petitioner uses those definitions if relevant. *See, e.g.*, EX1001, 3:60-66; 7:62-67; 14:65-15:5. For all other terms, Petitioner submits that no further construction is necessary and the challenged claims should be afforded a meaning “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

VIII. PERSON OF ORDINARY SKILL IN THE ART ("POSA")

A person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007); *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). As of the relevant priority date, a POSA in the relevant field would have had: (i) a Ph.D. in chemistry, biochemistry, medical chemistry, pharmacy, pharmaceutics, or a related field, and at least two years of relevant experience in drug development including an understanding of salt selection in drug development; (ii) a master's degree in the same fields and at least five years of the same relevant experience; or (iii) a bachelor's degree in the same fields and at least seven years of the same relevant experience. EX1002, ¶ 45. A POSA would also have knowledge of the scientific literature concerning the same as of the priority date. A POSA may also work as part of a multidisciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team to solve a given problem. *Id*. at ¶ 46.

IX. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(B))

Petitioner respectfully requests IPR of Claims 1-4, 17, 19, and 21-23 of the '708 patent on each specific ground of unpatentability outlined below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed

grounds, this Petition includes the declaration of a technical expert, Dr. Mukund Chorghade (EX1002), explaining what the art would have conveyed to a POSA. Dr. Chorghade is an expert in the relevant field. EX1003.

Ground	References	Basis[5]	Claims Challenged
1	WO '498	§ 102	1-3, 17, 19, 21-23
2	The '871 patent	§ 102	1-3, 17, 19, 21-23
3	WO '498	§ 103	3, 17, 19, 21-23
4	WO '498 and Bastin	§ 103	1-3, 17, 19, 21-23
5	WO '498, Bastin and Brittain	§ 103	4
6	WO '498 and Brittain	§ 103	4

The above-mentioned and other prior art references provide further background in the art and further motivation to combine the references, and/or further show a reasonable expectation of success in combining the teachings of the primary references to arrive at the claimed invention.

X. INVALIDITY ANALYSIS

A. Ground 1: Claims 1-3, 17, 19, and 21-23 Are Anticipated by WO '498

WO '498 (EX1004) anticipates Claims 1-3, 17, 19, and 21-23 of the '708 patent. To anticipate a patent claim, a prior art reference must disclose each element of the claim, explicitly or inherently, and enable one of ordinary skill in the art to practice the invention without undue experimentation. *See generally*, *Bristol-Myers*

[5] All references herein are to pre-AIA 35 U.S.C. §§ 102 and/or 103.

Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 368 (Fed. Cir. 2001). A "reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1381 (Fed. Cir. 2015).

Indeed, "[a] reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). "[I]t is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (C.C.P.A. 1968); *Mylan Pharmaceuticals Inc. v. Cosmo Technologies Ltd*., IPR2017-01035, Paper 17 at 8-9 (P.T.A.B. Sept. 21, 2017).

"[P]roof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1326 (Fed. Cir. 2005). For that matter, "anticipation does not require actual performance of suggestions in a disclosure." *Bristol-Myers Squibb*, 246 F.3d at 1379. In an IPR, prior art references are presumed to be enabled. *Google Inc. v.*

Jongerius Panoramic Techs, LLC, IPR2013-00191, Paper 70 at 37 (P.T.A.B. Aug. 12, 2014).

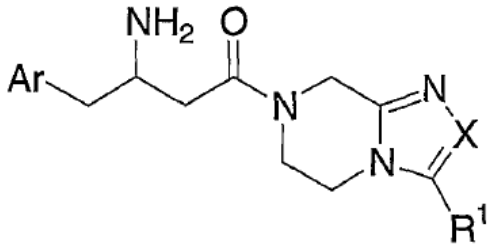
1. Disclosure of WO '498

WO '498 was published January 16, 2003, and is entitled "Beta-amino tetrahydroimidazo (1, 2-a) pyrazines and tetrahydrotrioazolo (4, 3-a) pyrazines as dipeptidyl peptidase inhibitors for the treatment or prevention of diabetes." WO '498 is, therefore, prior art to the '708 patent under 35 U.S.C. § 102(a).[6] WO '498

[6] Patent Owner has recently contended that at least Claims 1 and 2 are entitled to a priority date no later than December 13, 2001. *See supra*, FN 4. To the extent Patent Owner attempts to disqualify WO '498 as prior art under 35 U.S.C. § 102(a), as another Panel has noted, the development and presentation of such evidence is better left for trial. *Associated British Foods, PLC v. Cornell Research Foundation Inc*., IPR2019-00578, Paper 25 at 21 (P.T.A.B July 25, 2019). However, even assuming, *arguendo*, that Claims 1 and 2 are entitled to a priority date of December 13, 2001, WO '498 would be available as prior art to Claims 1 and 2 under 35 U.S.C. § 102(e)(2).

was not used by the Examiner during prosecution of the '708 patent to formulate any prior art rejection.[7]

WO '498 teaches compounds that may be used as dipeptidyl peptidase-IV enzyme inhibitors that may be used to treat or prevent diabetes. EX1004, 3:23-26. WO '498 teaches a number of compounds represented by genus formula I:

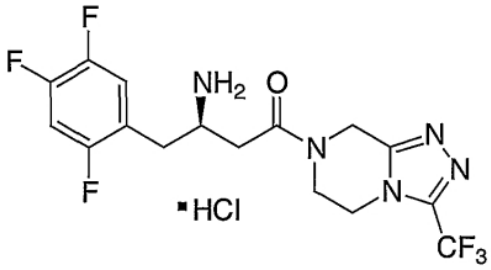


I

Id., 4:1-4. WO '498 exemplifies and claims 33 specific compounds that fall within genus formula I. For example, Example 7 depicts the hydrochloride salt of sitagliptin in its (R)-configuration:

[7] If Patent Owner contends that Petitioner has not made a sufficient showing that any printed publication cited in this Petition is not available as prior art under 35 U.S.C. § 102, Petitioner notes that all of the printed publications have conventional markers that indicate they were indeed published when and where they claim to have been published. *Provepharm Inc. v. Wista Laboratories Ltd.*, IPR2018-00182, Paper 16 at 13-18 (P.T.A.B. July 5, 2018).

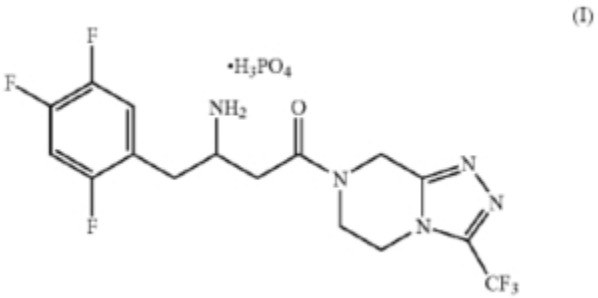
EXAMPLE 7



Id., 46:1-4. WO '498 also specifically claims sitagliptin and its "pharmaceutically acceptable salts thereof" as one of 33 compounds in Claim 15. EX1004, Claim 15 (7th compound), 55 (bottom compound). As to the meaning of "pharmaceutically acceptable salts," WO '498 teaches that the phosphoric acid salt is a "[p]articularly preferred" salt. *Id*., 10:14-15 ("[p]articularly preferred are citric, hydrobromic, hydrochloric, maleic, **phosphoric**, sulfuric, fumaric, and tartaric acids.") (emphasis added).

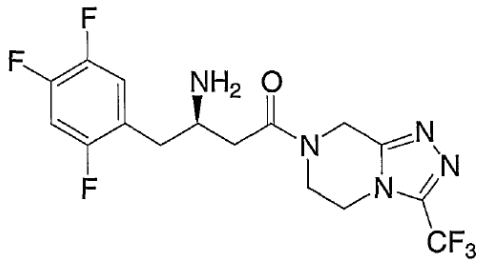
2. Claim 1

A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I:



or a hydrate thereof.

The ’708 patent openly admits that WO ’498 discloses sitagliptin and its pharmaceutically acceptable salts. EX1001, 1:49-57; *One World Technologies Inc*., IPR2017-00126, Paper 67 at 14 (“[T]he Court of Customs and Patent Appeals [has] long held that admissions in a patent may be considered prior art for any purpose.”). Consistent with the ’708 patent’s representations, WO ’498 claims (R)-sitagliptin and its “pharmaceutically acceptable salts thereof” as one of 33 compounds.



EX1004, Claim 15 (7th compound), 55 (bottom compound); *id*., 60:5 (“and pharmaceutically acceptable salts thereof”). *Perricone v. Medicis Pharmaceuticals Corp*., 432 F.3d 1368, 1376 (Fed. Cir. 2005) (“This court rejects the notion that one of these ingredients cannot anticipate because it appears without special emphasis in a longer list.”).

Patent Owner may point to Example 7 and argue that WO ’498 is limited to sitagliptin hydrochloride as it is specifically exemplified in the ’708 patent. EX1001, 4:19-23, 1:58-62 (“there is no specific disclosure in [WO ’498] of the newly discovered monobasic dihydrogen phosphate salt [sitagliptin].”). Not so. Claim 15

recites sitagliptin and its "pharmaceutically acceptable salts." EX1004, 60:5. WO '498 is not limited to just sitagliptin hydrochloride. *Syntex (U.S.A.) LLC v. Apotex Inc*., 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination"). Based on the claim language, "pharmaceutically acceptable salts" must at least include the accompanying "[p]articularly preferred" salts. EX1004, 10:14-15.

The complete list of accompanying "[p]articularly preferred" pharmaceutically acceptable salts is as follows: "ammonium, calcium, magnesium, potassium, and sodium salts" and "citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids." EX1004, 9:32, 10:14-15. Since WO '498 teaches the phosphoric acid salt is a "[p]articularly preferred" accompanying salt (*id*., 10:14-15), WO '498 teaches the phosphoric acid salt of sitagliptin. *Glaxo Group Ltd. v. Apotex, Inc*., 376 F.3d 1339, 1348 (Fed. Cir. 2004) ("[A]nticipation [only] requires that all limitations of the claimed invention are described in a single reference, rather than a single example in the reference.").[8]

[8] Even though Claim 1 refers to "dihydrogenphosphate salt" of sitagliptin, this is nothing more than another name for the (monobasic) phosphoric acid salt of sitagliptin. EX1001 at Title ("*Phosphoric acid salt* of a dipeptidyl peptidase-IV

inhibitor"); *id.,* 1:58 62 ("there is no specific disclosure in [WO '498] of the newly discovered monobasic dihydrogen phosphate salt [sitagliptin]."); *id*., Claim 21 (describing forming the compound of Claim 1 by contacting "one equivalent of [sitaglitin] . . . with about a one equivalent of phosphoric acid"—in other words a 1:1 sitagliptin to phosphoric acid salt); *id.,* 6:29-55 (describing the preparation of the dihydrogenphosphate salt using phosphoric acid).

Furthermore, the specification of the '708 patent explains, "the dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated 4-oxo-4-3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine cation and one molar equivalent of dihydrogenphosphate (biphosphate) anion." EX1001, 3:46-52; *id*., Claim 21 (1:1 sitagliptin to phosphoric acid salt). Thus, as the specification and claims make clear the dihydrogenphosphate salt of sitagliptin is nothing more than the *mono-protonated* (i.e., monobasic) amine cation of sitagliptin with its corresponding biphosphate anion, i.e., the phosphoric acid addition salt of sitagliptin. EX1002, ¶76 (explaining that sitagliptin base can *only* be mono-protonated at the primary amine, resulting in formation of the dihydrogenphosphate salt every time); EX1001, 1:58-62 ("there is no specific disclosure in [WO '498] of the newly discovered monobasic dihydrogen phosphate

In this regard, *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, which focuses on anticipation using prior art lists, is instructive. 683 F.3d 1356, 1361 (Fed. Cir. 2012). In *Wrigley*, the claim at issue covered chewing gum comprising, *inter alia*, two separate components: WS-23 and menthol. *Id*. at 1359. The anticipatory prior art (i.e., Shahidi) "list[ed] several categories of components that can be included in the compositions." *Id*. at 1360. Specifically, (prior art) Shahidi provided two separate lists: one list included WS-23 as a cooling agent, and the other list

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salt [sitagliptin]."). In this regard, Dr. Chorghade notes that the sitagliptin salt exemplified in WO '498 as Example 7 is a 1:1 salt. *See* EX1004 at 46:1-5 (Example 7, showing 1:1 sitagliptin HCl salt). EX1002, ¶76.

Finally, the Orange Book entries for Januvia® and Janumet® list the '708 patent. And the prescribing information labels for Januvia® and Janumet® refer to only "sitagliptin phosphate monohydrate" (without reference to "dihydrogenphosphate salt"). EX1014 at 9-10, EX1013 at 14 ("Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in JANUMET tablets in the form of sitagliptin phosphate monohydrate.") EX1013, at 14; EX1014, 10 ("Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base.")

included menthol as a flavoring agent. *Id*. In finding anticipation because the prior art "envisions using WS-23 and menthol in a single product" even though it disclosed "a number of different combinations of cooling and flavoring elements," *Wrigley* described the pertinent inquiry as follows:

> This is not a case in which the prior art reference merely discloses a genus and the claim at issue recites a species of that genus. In such a case, the issue of anticipation turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could "at once envisage" each member of the genus. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc*., 471 F.3d 1369, 1376 (Fed. Cir. 2006). **Shahidi specifically discloses WS-23 as a coolant and menthol as a flavoring agent. The question for purposes of anticipation is therefore whether the number of categories and components in Shahidi was so large that the combination of WS-23 and menthol would not be immediately apparent to one of ordinary skill in the art**.

Id. at 1361 (emphasis added); *Kennametal*, 780 F.3d at 1382 ("Because all the limitations of Kennametal's claim are specifically disclosed in Grab, the question for the purposes of anticipation is 'whether the number of categories and components' disclosed in Grab is so large that the combination of ruthenium and PVD coatings 'would not be immediately apparent to one of ordinary skill in the

art.'" (quoting *Wrigley*, 683 F.3d at 1361)); *Warner Chilcott Co. v. Teva Pharmaceuticals USA*, 89 F. Supp. 3d 641, 657 (D.N.J. 2015) ("[i]f the amount of combinations of explicitly named ingredients is a 'defined and limited class' and the amounts of the ingredients are within the prior art range, the result will be anticipated." (quoting *Wrigley*, 683 F.3d at 1361)).

Compare the instant case: WO '498 provides two closed lists; neither list leaves anything to the imagination. The primary list (i.e., Claim 15) provides 33 compounds, one of which is sitagliptin and its "pharmaceutically acceptable salts." And the secondary, and related (sub)list identifies by name the eight accompanying "[p]articularly preferred" pharmaceutically acceptable salts—one of which is the phosphoric acid salt. EX1004, 10:14-15. As WO '498 notes, "[i]t will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts." *Id*. at 10:16-17. *Kennametal*, 780 F.3d at 1383 ("At the very least, Grab's express 'contemplat[ion]' of PVD coatings is sufficient evidence that a reasonable mind could find that a person of skill in the art, reading Grab's claim 5, would immediately envisage applying a PVD coating.").

This is a stronger case of anticipation than *Wrigley*. In *Wrigley*, WS-23 (coolant) and menthol (flavoring agent) were on separate lists, and these two *separate and independent* components had to be selected from prior art Shahidi's

two lists. Here, sitagliptin base cation is not independent of its corresponding anionic salt (see EX1001, 3:46-52); it is the single compound, i.e., "sitagliptin phosphate." As Dr. Chorghade explains, a quaternary nitrogen cation (i.e., the sitagliptin ion) cannot exist without its accompanying anion (i.e., acid salt (phosphate ion)). EX1002, ¶79; EX1001, 3:46-52. Thus, WO '498's primary list and the accompanying secondary (sub)list collapse to form a single comprehensive list, which provides the complete list of compounds and their accompanying "pharmaceutically acceptable salts"—one of which is sitagliptin phosphate. EX1002, ¶80.

In rebuttal, no doubt Patent Owner will turn to *In re Petering* and its progeny, which dealt with genus anticipation. 301 F.2d 676, 681-682 (C.C.P.A. 1962). In *Petering*, the anticipatory reference "describe[d] to one skilled in this art not only the broad class but also [a] much more limited class within that broad class." *Id*. at 681. Based on stated preferences within the prior art reference, *Petering* found the POSA would envision 20 compounds from the broad genus. *Id*. at 682. From here, Patent Owner will likely provide the Panel with calculations to show that the two lists Petitioner uses from WO '498 result in more than 20 compounds.

As explained above, the primary list and the accompanying secondary (sub)list of WO '498 collapse to form a single comprehensive list whereas *Petering* dealt with genus anticipation. "For the purposes of whether they are anticipatory,

lists and genera are often treated differently under our case law." *In re Gleave*, 560 F.3d 1331, 1337 (Fed. Cir. 2009). When dealing with lists, the number is irrelevant. *Id*. at 1338 ("[]Wraight expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP-2, and under our precedent, this list anticipates Gleave's claims."); *id*. at 1333 ("[Wraight's] list include[d] **more than 1400 sequences**.") (emphasis added).

WO '498 exactly depicts (and claims) the dipeptidyl peptidase-IV inhibitor structures in a primary list and calls out, by name, their "[p]articularly preferred" salts in the accompanying secondary list. Together, they form a single comprehensive list of compounds one of which is (R)-sitagliptin phosphate. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put into the last opening in a jig-saw puzzle. It is not invention." *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 335 (1945). Claim 1 is anticipated.

3. Claim 2

Claim 2 recites the same compound of formula I as Claim 1 but recites the (R)-configuration. As stated above, WO '498 depicts the (R)-configuration of sitagliptin in Claim 15 (7^{th} compound)/Example 7. The discussion of Claim 1 is incorporated herein. Therefore, (R)-sitagliptin phosphate is disclosed and Claim 2 is anticipated.

4. Claim 3

Claim 3 recites the same compound of formula I as Claim 1 but recites the (S)-configuration of the compound. (R)-sitagliptin phosphate is anticipated for the reasons discussed above. The discussion of Claim 1 is incorporated herein.

WO '498 taught "[t]he compounds of the instant invention have **one** asymmetric center at the beta carbon atom" and "[e]ach such asymmetric center will independently produce **two** optical isomers and **it is intended that all of the possible optical isomers…are included within the ambit of this invention**." EX1004, 8:21-22, 24-27 (emphasis added). Even with respect to the Examples, WO '498 states: "Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following *Examples* and pharmaceutically acceptable salts thereof **and individual diastereomers thereof**." EX1004, 11:11-14 (emphasis added). Therefore, WO '498 teaches the (S)-configuration of the sitagliptin since Example 7 is sitagliptin.

WO '498 therefore taught that there were only *two* optical isomers of sitagliptin phosphate, i.e., (R) and (S), and explained how to synthesize them. EX1004, 8:21-22, 24-27; 9:24-26. Therefore, the skilled artisan would have immediately envisaged (S)-sitagliptin phosphate. *Petering*, 301 F.2d at 681-682. Accordingly, Claim 3 is anticipated.

5. Claim 17

a) A pharmaceutical composition comprising

WO ’498 teaches pharmaceutical compositions comprising the disclosed compounds. EX1004, Claim 16, 3:26-27 (“The invention is also directed to pharmaceutical compositions comprising these compounds.”), 11:26-29, 12:10-12.

b) a therapeutically effective amount of the salt according to claim 2

“[T]he salt according to claim 2,” i.e., (R)-sitagliptin phosphate, is taught by WO ’498 as explained above. WO ’498 teaches administering “a therapeutically effective amount” of its compounds. *See, e.g.*, Claims 19-33 of WO ’498. WO ’498 further defines “a therapeutically effective amount” as “the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.” EX1004, 11:32-35, 13:21-33 (explaining the compounds “have utility in the treatment of type II diabetes.”), 12:18-13:19 (stating that “the compounds of the following examples had activity inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays.”).[9] Therefore, WO ’498 teaches a therapeutically effective amount of (R)-sitagliptin phosphate.

[9] Example 7 is sitagliptin hydrochloride.

c) in association with one or more pharmaceutically acceptable carriers.

WO ’498 specifically teaches “the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention **and a pharmaceutically acceptable carrier**.” EX1004, 12:10-12 (emphasis added), 20:10-16; 20:21-23. Accordingly, WO ’498 anticipates Claim 17.

6. Claim 19

a) A method for the treatment of type 2 diabetes comprising

WO ’498 teaches compounds “which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes.” EX1004, 3:24-26, 13:28-30.

b) administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.

WO ’498 teaches administration of the disclosed compounds: “The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme **in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound**.” EX1004, 11:15-17 (emphasis added). As discussed above with regard to Claim 17, WO ’498 also teaches “a therapeutically effective amount of the salt according to claim 2.” *See,*

e.g., EX1004, Claim 19; 11:32-35. That discussion is incorporated herein. WO '498 teaches every element of Claim 19. Accordingly, WO '498 anticipates Claim 19.

7. Claims 21-22

21. A process for preparing the salt of claim 2 comprising the step of contacting one equivalent of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100° C.

WO '498 teaches obtaining sitagliptin salts by the same process described and claimed in the '708 patent, i.e., combining sitagliptin with an acid in an organic solvent at ambient temperature.[10] EX1004, Example 7. WO '498 discloses using methanol, i.e., an organic solvent. EX1004, 38:19.

As Dr. Chorghade notes, the sitagliptin salt exemplified in WO '498 as Example 7 is a 1:1 salt. *See* EX1004 at 46:1-5 (Example 7, showing 1:1 sitagliptin HCl salt); EX1002, ¶99. Example 7, step B teaches that the salt form is prepared in a manner "analogous" to Example 1, step D—the triazolo pyrazine compound, i.e.,

[10] "Ambient temperature" is well known as equivalent to room temperature or about 25˚C.

sitagliptin base, is reacted with a non-toxic acid. EX1004, Example 7. This reaction necessarily involves contacting the sitagliptin base molecule with the acid molecule, in order to form the salt. In other words, "*contacting* one equivalent of [sitagliptin] … with about a one equivalent of [ ] acid" in the reaction as recited by Claim 21.[11] EX1001, Claim 21; EX1002, ¶99. While Example 7 prepares a hydrochloride salt, WO '498 discloses that the phosphoric acid is a "particularly preferred" acid for the preparation of acid addition salts. *Id.* at 10:8-15. Further, Example 7 teaches that in the presence of acid, sitagliptin forms a 1:1 salt (compare Examples 1-5 teaching that other exemplified compounds of WO '498 form dihydrochlorides).

Accordingly, WO '498, which exemplifies the preparation of a 1:1 sitagliptin salt and discloses that the phosphoric acid is a "particularly preferred" acid for the

[11] In fact, the '708 patent's specification explains "the dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated 4-oxo-4-3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine cation and one molar equivalent of dihydrogenphosphate (biphosphate) anion." EX1001, 3:46-52. Thus, the formation of sitagliptin phosphate requires "contact" between "one equivalent" of sitagliptin with "one equivalent" phosphoric acid because the sitagliptin can only interact with "one equivalent" phosphoric acid.

preparation of acid addition salts, discloses the claimed process and anticipates Claim 21.

Claim 22 simply narrows the type of organic solvent required by the process of Claim 21 to a C_1 alcohol. WO '498 discloses using methanol, i.e, a C_1 alcohol. EX1004, 38:19. Therefore, Claim 22 is anticipated.

8. Claim 23

Claim 23 recites the sitagliptin phosphoric acid salt produced by the process of Claim 21. A product-by-process claim defines a product in terms of how the product was made. *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). Claim 23 is therefore a product-by-process claim, reciting the product produced by the process of Claim 21. Claim 21 further depends from Claim 2. As explained above, the product of Claim 2, is anticipated. Unless the process limitations (in a product-by-process claim) imparts some unique and novel property or structure in the resulting product, the process limitations are not accorded any weight for determining validity. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012); *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009).

Nothing in the '708 patent suggests that any functional or structural difference is imparted upon the product of Claim 23 by the process limitations of Claim 21.

EX1002, ¶ 103. Accordingly, the process limitations of Claim 21 carry no patentable weight for determining the validity of Claim 23. Therefore, Claim 23 is anticipated.

B. Ground 2: Claims 1-3, 17, 19 and 21-23 Are Anticipated by the '871 Patent

1. Disclosure of the '871 Patent

U.S. 6,699,871 (EX1007) claims priority to U.S. Provisional Application 60/303,474 (filed July 6, 2001) (EX1012). Since the application that led to the '871 patent was filed before the application that led to the '708 patent (i.e., U.S. Provisional Application No. 60/482,161, filed on June 24, 2003), the '871 patent is

prior art to the '708 patent under 35 U.S.C. § 102(e)(2).[12, 13, 14] *Associated British Foods, PLC*, IPR2019-00578, Paper 25 at 17. Likewise, WO '498 claims priority to

[12] Petitioner also notes that the utility application that led to the '871 patent (i.e., U.S. App. 10/189,603 (filed July 5, 2002)) was also filed before the provisional application that led to the '708 patent.

[13] The '871 patent is "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." The '871 patent is "by another" because it shares no inventor overlap with the '708 patent. *In re Fong*, 378 F.2d 977, 980 (CCPA 1967) ("A [reference] is considered 'to another' when the 'inventive entities' are different."); *Watson Labs., Inc. v. United Therapeutics Corp*., IPR2017-01621, Paper 10 at 12 (P.T.A.B. Jan. 11, 2018).

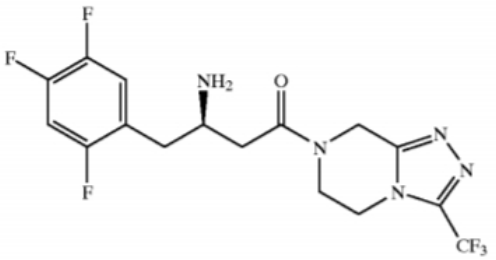
[14] Patent Owner has recently contended that at least Claims 1 and 2 are entitled to a priority date no later than December 13, 2001. *See supra*, FN 4. However, even assuming, *arguendo*, that Claims 1 and 2 are entitled to a priority date of December 13, 2001, the '871 patent would be available as prior art to Claims 1 and 2 under 35 U.S.C. § 102(e)(2).

this same U.S. provisional application. EX1004, cover page. The specifications of the '871 patent and WO '498 are identical in all relevant material respects.[15] .[16]

2. Claims 1 and 2

Claims 1 and 2 of the '708 patent are reproduced above at Ground 1. Besides having the same specification in all material aspects as WO '498, the '871 patent also teaches Claim 17 which claims (R)-sitagliptin "or a pharmaceutically acceptable salt thereof" and is reproduced below:

17. A compound which is:



or a pharmaceutically acceptable salt thereof.

[15] To the extent Patent Owner attempts to disqualify the '871 patent as prior art, as another Panel has noted, the development and presentation of such evidence is left for trial. *Associated British Foods, PLC,* IPR2019-00578, Paper 25 at 21.

[16] Petitioner notes that the '871 patent is listed on the face of the '708 patent but was not used by the Examiner for any prior art rejection during prosecution of the application which became the '708 patent.

EX1007, 41:1-14.

Since Claim 17 recites "or a pharmaceutically acceptable salt thereof," the inventors of the '871 patent meant to cover more than the exemplified (singular) HCl salt. EX1007, 25:55-32:45 (Examples 1-7). At the very least "or a pharmaceutically acceptable salt thereof" must include the "[p]articular preferred" pharmaceutically acceptable salts taught by the '871 patent, which includes the phosphoric acid salt. EX1007, 7:2-4. Since the '871 patent teaches the phosphoric acid salt is a "[p]articularly preferred" accompanying salt, the '871 patent teaches the phosphoric acid salt of sitagliptin. *Glaxo Group Ltd. v. Apotex, Inc*., 376 F.3d 1339, 1348 (Fed. Cir. 2004). Therefore, Claims 1 and 2 of the '708 patent are anticipated.

3. Claim 3

Claim 3 recites (S)-sitagliptin phosphate of the compound. The '871 patent taught "[t]he compounds of the instant invention have **one** asymmetric center at the beta carbon atom" and "[e]ach such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers…are included within the ambit of this invention." EX1007, 5:53-61 (emphasis added). Even with respect to the Examples, the '871 patent states: "Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof **and individual diastereomers thereof**."

EX1007, 7:48-52 (emphasis added). Therefore, the '871 patent teaches the (S)-configuration of the sitagliptin since Example 7 is (R)-sitagliptin.

For that matter, since there is only "one asymmetric center at the beta carbon atom" upon the disclosure of (R)-sitagliptin phosphate, the skilled artisan would have immediately envisaged (S)-sitagliptin phosphate, i.e., the only other possible isomer. *Petering*, 301 F.2d at 681-682. Accordingly, Claim 3 is anticipated.

4. Claims 17 and 19

Regarding Claims 17 and 19 of the '708 patent, based on the claims and disclosures of the '871 patent, the claims are anticipated as shown in the chart below:

17. A pharmaceutical composition comprising	EX1007, 3:2-6 ("The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of Such diseases in which the dipeptidyl peptidase IV enzyme is involved"); 14:10-13 ("The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy"); 14:29-33 ("The pharmaceutical compositions containing the active ingredient may be in a form Suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily Suspensions, dispersible powders or granules, emulsions, hard or Soft capsules, or syrups or elixirs"); Claim 18 ("A pharmaceutical composition which comprises an inert carrier and a compound of claim 1")

a therapeutically effective amount of the salt according to claim 2	*See* analysis of Claim 2 above; EX1007, 8:9-13 ("The term 'therapeutically effective amount' means the amount of the Subject compound that will elicit the biological or medical response of a tissue, System, animal or human that is being Sought by the researcher, Veterinarian, medical doctor or other clinician"); Claims 22 and 23 ("administering to the patient a therapeutically effective amount").
in association with one or more pharmaceutically acceptable carriers	EX1007, 14:3-4 ("conventional non-toxic pharmaceutically acceptable carriers"); Claim 18 ("A pharmaceutical composition which comprises an inert carrier and a compound of claim 1").
19. A method for the treatment of type 2 diabetes comprising	EX1007, 2:64-3:2 ("The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ('DP-IV inhibitors') and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, Such as diabetes and particularly type 2 diabetes"); Claim 22 ("A method for treating or controlling diabetes in a mammalian patient in need thereof comprising the administration to a patient of an effective amount of a compound of claim 1"); Claim 23 ("A method for treating or controlling non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of claim 1").
administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.	*See* analysis of Claim 2 above; EX1007, 8:9-13 ("The term 'therapeutically effective amount' means the amount of the Subject compound that will elicit the biological or medical response of a tissue, System, animal or human that is being Sought by the researcher, Veterinarian, medical doctor or other clinician");

	Claims 22 and 23 ("administering to the patient a therapeutically effective amount").

EX1002, ¶114.

Therefore, Claims 17 and 19 are anticipated.

5. Claims 21-23

Claim 21 is reproduced above at Ground 1. The '871 patent teaches obtaining sitagliptin salts by the same process described and claimed in the '708 patent, i.e., combining sitagliptin with an acid in an organic solvent at ambient temperature.[17] The '871 patent discloses using methanol, i.e., an organic solvent. *See* EX1007, 32:1-42.

For the same reasons explained *supra*, Ground 1, Claim 21, the sitagliptin salt exemplified in the '871 patent at Example 7 is a 1:1 salt. EX1007, 7:2-4. Like WO '498, the '871 patent also discloses that the phosphoric acid is a "particularly preferred" acid for the preparation of acid addition salts. EX1007, 7:2-4. As explained at Ground 1, the salt formation reaction necessarily involves contacting the sitagliptin base molecule with the acid molecule, in order to form the salt. In

[17] As Dr. Chorghade explains, "ambient temperature" is well known as equivalent to room temperature or about 25˚C. EX1002, ¶98.

other words, "*contacting* one equivalent of [sitagliptin] … with about a one equivalent of [ ] acid" in the reaction as recited by Claim 21. EX1001, Claim 21.

Accordingly, the '871 patent, which exemplifies the preparation of a 1:1 sitagliptin salt and discloses that the phosphoric acid is a "particularly preferred" acid for the preparation of acid addition salts, discloses the claimed process and anticipates Claim 21.

Claim 22 simply narrows the type of organic solvent required by the process of Claim 21 to methanol. The '871 patent discloses using methanol, i.e, an organic solvent. EX1007, 32: 1-40. Accordingly, Claim 22 is anticipated.

Claim 23 recites the sitagliptin phosphoric acid salt produced by the process of Claim 21. Claim 23 is a product-by-process claim, reciting the product of Claim 21. As explained *supra*, the product of Claim 23 is anticipated. Further, as explained above in Ground 1, the process limitations impart no functional or structural difference upon the product of Claim 23, and therefore carry no patentable weight. *In re Thorpe*, 777 F.2d at 697; *Amgen Inc.*, 580 F.3d at 1369; *Greenliant Sys.*, 692 F.3d at 1268. Accordingly, Claim 23 is anticipated.

C. Ground 3: Claims 3, 17, 19, and 21-23 Would Have Been Obvious in View of WO '498[18]

[18] To the extent the panel finds any claim is anticipated, then it is also rendered obvious. *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019).

The inquiry for obviousness was established in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). The *Graham* factors require an examination of: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness. The obviousness analysis looks to the state of the art that existed at the time the invention was made. *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965). Moreover, "[o]bviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

1. The Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the art has been described above. *Supra* at VIII.

2. The Scope and Content of the Prior Art

a) WO '498 (EX1004)

WO '498 has been described above. *Supra* at X.A.1.

b) Claim 3

As explained in Ground 1, *supra*, WO '498 anticipates Claims 1-3, 17, 19, and 21-23. If, however, the Panel concludes that only Claims 1 and 2 are anticipated, then Claims 3, 17, 19, and 21-23 would have been obvious in view of WO '498 alone. As explained above, Claims 1 and 2 recite sitagliptin phosphate and (R)-sitagliptin phosphate, respectively. If the panel concludes that Claims 1 and 2

are anticipated by WO '498, then it follows that (R)-sitagliptin phosphate is necessarily a prior art compound. Upon making the predicate finding that (R)-sitagliptin phosphate was a prior art compound, then Claims 3, 17, 19, and 21-23 would have been obvious in view of WO '498 alone.

At the outset, the PTAB's use of a predicate anticipation finding and that finding's impact on the obviousness of related dependent claims is nothing new. For example, in *Hologic Inc. v. Becton, Dickinson and Co*., the PTAB used this methodology. IPR2016-00820, Paper 52 at 5-7, 25, 27-33 (P.T.A.B. Sept. 28, 2017) (predicate finding of anticipation by Fish of certain claims needed for obviousness of related dependent claims); *id*. at 25 ("This argument is not persuasive because Petitioner, in fact, has shown Fish anticipates the challenged independent claims, as discussed above").[19]

As explained above, the '708 patent admits that at least sitagliptin and its "pharmaceutically acceptable salts" are in the prior art. EX1001, 1:49-57; *One World Technologies Inc.*, IPR2017-00126, Paper 67 at 14-15. Consistent with this admission, if the PTAB concludes that Claims 1 and 2 are anticipated for the reasons

[19] Indeed, *Hologic* even expressly acknowledged the impact of its predicate anticipation finding on obviousness of related dependent claims in the context of secondary considerations. *Id*. at 30.

stated in Ground 1 (incorporated by reference), then (R)-sitagliptin phosphate is necessarily a prior art compound.

Claim 3 then recites the **only** other possible isomer of (R)-sitagliptin phosphate, i.e., (S)-sitagliptin phosphate, and WO '498 taught the (S)-configuration. EX1002, ¶123; EX1004, 8:21-22 ("[t]he compounds of the instant invention have one asymmetric center at the beta carbon atom" and "[e]ach such asymmetric center will independently produce two optical isomers."); 8:24-27; 11:11-14. In other words, WO '498 taught that there were only *two* possible isomers of sitagliptin, i.e., (R) and (S), and explained how to synthesize each of them. EX1004, 8:21-22, 24-27; 9:24-26.

The fact that the (R) and (S) configurations are taught in the same paragraphs itself provides sufficient motivation to make the (S) configuration. *Boston Scientific Scimed, Inc. v. Cordis Corp*., 554 F.3d 982, 991 (Fed. Cir. 2009) ("Combining two embodiments disclosed adjacent to each other in a prior art patent does not require a leap of inventiveness."). Moreover, a POSA would have had a reasonable expectation for synthesizing the (S)-configuration of a known compound given WO '498 tells the skilled artisan how to do it. EX1002, ¶124; EX1004, 9:24-26. Accordingly, Claim 3 would have been obvious.

c) Claim 17

(1) A pharmaceutical composition comprising

WO ’498 teaches pharmaceutical compositions comprising the disclosed compounds. EX1004, Claim 16; 3:26-27; 11:26-29; 12:10-12. Given WO ’498 teaches the compounds are active (EX1004, 12:18-13:19), it would have been obvious to make a pharmaceutical composition with a reasonable expectation of success. EX1002, ¶125.

(2) a therapeutically effective amount of the salt according to claim 2

As explained above, the predicate finding for Ground 2 is that Claim 2 is anticipated. As to the remaining limitations, WO ’498 teaches administering “a therapeutically effective amount” of the compounds for a variety of treatments. *See, e.g.*, EX1004, Claims 19-33, 11:32-35, 13:21-33.

(3) in association with one or more pharmaceutically acceptable carriers.

WO ’498 specifically teaches “the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and **a pharmaceutically acceptable carrier**.” EX1004, 12:10-12 (emphasis added). *See also id.* at 20:10-16; 20:21-23. Accordingly, Claim 17 would have been obvious.

d) Claim 19

(1) A method for the treatment of type 2 diabetes comprising

WO '498 teaches compounds "which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes." EX1004, 3:24-26; 13:28-30.

(2) administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.

WO '498 teaches administration of the disclosed compounds. EX1004, 11:15-17. As discussed above with regard to Claim 17, WO '498 also teaches "a therapeutically effective amount of the salt according to claim 2." In view of the teachings of WO '498, the POSA would have had a reasonable expectation of success. Accordingly, Claim 19 would have been obvious.

e) Claims 21-23

To the extent these claims are not found to be anticipated for the reasons explained at Grounds 1 and 2, they would have been obvious. Claim 21 recites the process of making the compound of Claim 2.

As explained at Ground 1, Claim 21, the sitagliptin salt exemplified in WO '498 as Example 7 is a 1:1 salt. *See* EX1004 at 46:1-5 (Example 7, showing 1:1 sitagliptin HCl salt); EX1002, ¶132. Example 7, step B teaches that the salt form is prepared in a manner "analogous" to Example 1, step D— the triazolo pyrazine compound, i.e., sitagliptin base, is reacted with a non-toxic acid. *Id.*; EX1004, Example 7. This reaction necessarily involves contacting one sitagliptin base

molecule with one acid molecule, in order to form the salt. *See* discuss *supra*, Ground 1, Claim 21. In other words, "*contacting* one equivalent of [sitagliptin] … with about a one equivalent of [ ] acid" in the reaction as recited by Claim 21. EX1001, Claim 21. While Example 7 prepares a hydrochloride salt, WO '498 also discloses that the phosphoric acid is a "particularly preferred" acid for the preparation of acid addition salts. *Id.* at 10:8-15. Therefore, a POSA would have been motivated to substitute the hydrogen chloride, taught by Example 7 of WO '498, for phosphoric acid, taught as "preferred" also by WO '498, with a reasonable expectation of success. *Id.*; EX1002, ¶132. Further, as Dr. Chorgarde explains, Example 7 teaches that in the presence of acid, sitagliptin forms a 1:1 salt (compare Examples 1-5 teaching that other exemplified compounds of WO '498 form dihydrochlorides). EX1002, ¶132.

As Dr. Chorghade explains, it would have been nothing more than routine experimentation to optimize the reaction variables to arrive at the phosphoric acid addition salt, based on the preferred salts taught by WO '498 and the synthetic protocols disclosed therein. EX1002, ¶133; *In re Aller*, 220 F.2d 454, 456-57 (C.C.P.A. 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

WO '498 further teaches that the reaction proceeds at "ambient temperature," i.e., room temperature or about 25˚ C. EX1002, ¶134; EX1004, 38:20. Claim 21 recites "about 25-100°C." Overlapping ranges establish a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003).[20] WO '498 further teaches that the reaction occurs in methanol, i.e., an organic solvent. EX1002, 134; EX1004, 38:19. Accordingly, Claim 21 would have been obvious.

Claim 22 simply narrows the type of organic solvent required by the process of Claim 21 to "a C1-C5 linear or branched alkanol." WO '498 teaches that the reaction occurs in methanol, i.e., a C_1 alcohol. EX1002, ¶135; EX1004, 38:19. Accordingly, Claim 22 would have been obvious.

[20] To the extent Patent Owner contends that room temperature is slightly below "about 25[]˚C," Petitioner notes the disclosure of adjacent range supports obviousness. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). In any event, as the MPEP § 2144 ("II. ROUTINE OPTIMIZATION") explains, "[g]enerally, **differences in . . . temperature will not support the patentability** of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." (emphasis added). There is no showing of criticality in the '708 patent or its related file history as to the temperature of the reaction.

Claim 23 merely recites the product, i.e., (R)-sitagliptin phosphate. Therefore, for the same reasons (R)-sitagliptin phosphate would have been anticipated, as discussed above at Ground 1, Claim 2, Claim 23 would have been obvious as a product-by-process claim. *Amgen Inc.*, 580 F.3d at 1369 ("a product-by-process claim is anticipated by or obvious from prior art products").

D. Ground 4: Claims 1-3, 17, 19, and 21-23 Would Have Been Obvious in View of WO '498 and Bastin

1. The Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the art has been described above. *Supra* at VIII.

2. The Scope and Content of the Prior Art

a) WO '498 (EX1004)

WO '498 has been described above. *Supra* at X.A.1.

b) Bastin (EX1006)

Bastin et al., "Salt Selection and Optimisation [sic] Procedures for Pharmaceutical New Chemical Entities," 4 *Organic Process Research & Development*, 427-435, was published in 2000 ("Bastin"). Bastin is prior art to the '708 patent under 35 U.S.C. § 102(b).[21] Bastin was not disclosed to the Examiner

[21] Patent Owner has recently contended that at least Claims 1 and 2 are entitled to a priority date no later than December 13, 2001. *See supra*, FN 4. Regardless, Bastin is prior art under 35 U.S.C. § 102(b), available for all asserted claims.

or cited by the Examiner during prosecution of the application which issued as the '708 patent. Bastin teaches commonly used salts:

Table 1. **Classification of common pharmaceutical salts**

salt class	examples
	Anions
inorganic acids	hydrochloride, hydrobromide, sulfate, nitrate, phosphate
sulfonic acids	mesylate,[b] esylate,[c] isethionate,[d] tosylate,[e] napsylate,[f] besylate[g]
carboxylic acids	acetate, propionate, maleate, benzoate, salicylate, fumarate
anionic amino acids	glutamate, aspartate
hydroxyacids	Citrate, lactate, succinate, tartrate, glycollate
fatty acids	hexanoate, octanoate, decanoate, oleate, stearate
insoluble salts	pamoate (embonate), polystyrene sulfonate (resinate)
	Cations
organic amines	triethylamine, ethanolamine, triethanolamine, meglumine, ethylenediamine, choline
insoluble salts	procaine, benzathine
metallic	sodium, potassium, calcium, magnesium, zinc
cationic amino acids	arginine, lysine, histidine

[a] Based on data from various sources.[9–11] [b] Methane sulfonate. [c] Ethane sulfonate. [d] 2-Hydroxyethane sulfonate. [e] Toluene sulfonate. [f] Naphthalene sulfonate. [g] Benzene sulfonate.

Id., 428.

Bastin teaches that:

> The vast majority of salts are developed to enhance the aqueous solubility of drug substances. **For weakly basic drug substances, salts of an inorganic acid (e.g., hydrochloride, sulphate, or phosphate)**, a sulphonic acid (mesylate or isethionate), a carboxylic acid (acetate, maleate or fumarate), a hydroxyacid (citrate or tartrate), or possibly an amino acid (arginine or lysine) could be considered.

Id. (emphasis added).

3. The Differences Between the Claims and Prior Art

a) Claim 1

(1) There Is No Requirement to Select a Lead Compound in Salt Selection Cases

WO '498 claims (R)-sitagliptin and its "pharmaceutically acceptable salts thereof" as one of 33 compounds. EX1004, 55 (bottom compound); *id*., 60:5 ("and pharmaceutically acceptable salts thereof"). Presumably pointing to structural obviousness case law (or some other lead selection variant) where the Federal Circuit requires selecting a lead compound or compounds for further structural modification, Patent Owner may argue that the POSA would not have selected (R)-sitagliptin in the first place from the 33 compounds disclosed in WO '498. *See, e.g., Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-93 (Fed. Cir. 2012). From there, Patent Owner will argue that Petitioner's obviousness grounds fail.[22]

[22] In rebutting obviousness, Patent Owner may argue that the skilled artisan would not have been motivated to even use WO '498 in the first place. Rather, Patent Owner may argue that the skilled artisan would have selected some other compound from some other reference, a commercialized compound, or a compound in clinical trials. The Federal Circuit and PTAB have routinely rejected such arguments. *Bayer Pharma AG v. Watson Laboratories, Inc*., 874 F.3d 1316 (Fed. Cir. 2017); *Amneal Pharm. LLC v. Purdue Pharma L.P.*, IPR2016-01412, Paper 9 at 15 (P.T.A.B.

This, however, is not a structural obviousness case; this is a salt selection case. In this regard, the Federal Circuit's discussion in *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348 (Fed. Cir. 2007) which dealt with obviousness in the context of salt selection is instructive. In *Pfizer*, Pfizer's U.S. Patent No. 4,879,303 ("the '303 patent") was directed, *inter alia*, to a specific compound, i.e., "[t]he besylate salt of amlodipine." *Id*. at 1356. Amlodipine besylate is an acid addition salt form of amlodipine, formed from the reaction of amlodipine, a weak base, and benzene sulphonic acid. *Id*. at 1353.

Pfizer found the besylate salt form of amlodipine would have been obvious over U.S. Patent No. 4,572,909 ("the '909 patent"). *Id*. at 1352-53. The '909 patent is attached for the PTAB's review. EX 1011. Although the '909 patent exemplified a number of compounds, like WO '498, there is no particular focus on amlodipine over the other exampled compounds. *See, e.g.*, *id*. at 1353 ("The '909 patent claims certain dihydropyridine compounds and their pharmaceutically-acceptable acid addition salts."). But unlike WO '498 which discloses the phosphate salt, the

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Feb. 14, 2017); *Gnosis SPA v. South Alabama Medical Science Foundation*, IPR2013-00116, Paper 68 at 12 (P.T.A.B. June 20, 2014); *Celanese Int'l Corp. v. Daicel Corp.*, IPR2017-00163, Paper 46 at 25 (P.T.A.B. May 3, 2018).

'909 patent did not disclose the besylate salt—and yet *Pfizer* still found the claims of the '303 patent invalid. *Id*. at 1361-62.

A complete review of *Pfizer* shows no discussion whatsoever by the Federal Circuit of any requirement to show that amlodipine would have stood out to the POSA from the disclosure of the '909 patent. Therefore, any effort by Patent Owner to graft any kind of lead compound selection in a salt selection case is contrary to applicable Federal Circuit precedent. *Mylan Pharmaceuticals Inc. et al. v. UCB Pharma GMBH*, IPR2016-00510, Paper No. 45 at 47 (P.T.A.B. July 19, 2017) (explaining that *Pfizer* dealt with a situation where "the prior art there disclosed the base compound and a number of its salt forms."). Thus, under *Pfizer*, Petitioner need only show that (R)-sitagliptin and its "pharmaceutically acceptable salts thereof" are disclosed by WO '498.

Patent Owner cannot dispute that WO '498 claims (R)-sitagliptin and its "pharmaceutically acceptable salts thereof" as one of 33 compounds. And as mentioned above, the '708 patent plainly admits in the "Background of the Invention" that WO '498 "specifically disclosed . . . 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine [and its] [p]harmaceutically acceptable salts." EX1001, 1:49-57. *One World Technologies Inc.*, IPR2017-00126, Paper 67 at 14-15; *In re Nomiya*, 509 F.2d at 570-71 (C.C.P.A. 1975) ("We see no reason why appellants'

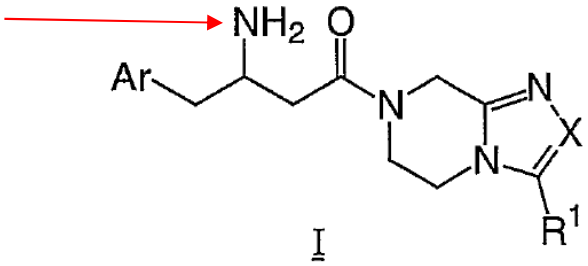
representations in their application should not be accepted at face value as admissions that Figs. 1 and 2 may be considered 'prior art' for any purpose."); *Constant*, 848 F.2d at 1570; *In re Fout*, 675 F.2d 297, 300 (C.C.P.A. 1982).

(2) WO '498 and Bastin Would Have Rendered the Phosphoric Acid Salt Obvious

Since WO '498 discloses (R)-sitagliptin and its "pharmaceutically acceptable salts," the skilled artisan would have been motivated to optimize the salt. *Pfizer*, 480 F.3d at 1368 ("the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt.").

As Dr. Chorghade explains, from the disclosure of (R)-sitagliptin and its "pharmaceutically acceptable salts," the POSA would next turn to the Examples and note that *in every case*, the salt represented was hydrochloride salt, i.e., an "*acid* salt." EX1002, ¶145. This is expected because as WO '498 teaches, "[w]hen the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids." EX1004, 10:8-10. Reviewing the synthetic schemes and in particular the schemes that correspond to making

sitagliptin (i.e., Example 7), the POSA would have known sitagliptin is basic due to the presence of the -NH_2 (amino) group[23] seen in the general formula below:



I

EX1002, ¶147; EX1004, 28; 38:15-23 (Step D of Example 1 showing reaction of the "amino" group with HCl).[24]

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[23] As Dr. Chorgarde explains, amines are well known to be weakly basic. *See, e.g.*, EX1016, 616-617 (explaining that weak bases include compounds containing a nitrogen atom, such as amines)); EX1002, ¶147.

[24] To the extent Patent Owner argues that WO '498 discloses other "[p]articularly preferred" salts such as "ammonium, calcium, magnesium, potassium, and sodium salts" (EX1004, 9:30-31), as Dr. Chorghade explains, this group constitutes *basic* salts, not the *acid* salts. EX1002, fn. 19. The reaction schemes of WO '498 result in a basic compound bearing an amino group. Based on the teachings of WO '498, the skilled artisan would first turn to the other *acid* salts. EX1004, 10:8-10 ("When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids."); EX1002, ¶148.

Turning to possible alternatives for the hydrochloride *acid* salts: WO '498 teaches that the other alternative "[p]articularly preferred" *acid* salts would be the following list of seven salts: citric, hydrobromic, maleic, **phosphoric**, sulfuric, fumaric, and tartaric acids. EX1004, 10:14-15 (emphasis added).

A POSA would also look to Bastin. EX1002, ¶150. The POSA would be motivated to combine the teachings of WO '498 and Bastin because Bastin deals with salt selection and optimization procedures for pharmaceutical new chemical entities. *See* EX1006, Title. Furthermore, Bastin would have given the POSA motivation to make alternatives to the hydrochloride salt due to its potential problems such as "unacceptably high acidity in formulations (e.g., parenteral products), the risk of corrosion, less than optimal solubility due to the risk of salting out and the potential for poor stability if the drug is acid labile and hygroscopic." EX1002, fn. 20; EX1006 at 428.

Bastin teaches that "[f]or weakly basic drug substances, salts of an inorganic acid (e.g., hydrochloride, sulphate, or phosphate) . . . could be considered." EX1006 at 428. As explained *supra*, sitagliptin contains an amine group which would make the drug substance weakly basic. *See* EX1002, ¶150. Accordingly, a POSA would have been motivated to combine the inorganic acids taught by Bastin with the sitagliptin taught by WO '498.

Bastin provides a list of "inorganic acids" which are "common pharmaceutical salts": "hydrochloride, hydrobromide, sulfate, nitrate, phosphate" at Table 1. *Id*. Cross-referencing this list from Bastin with the seven "[p]articularly preferred" acid salts provided in WO '498, a POSA would have known that both lists included the hydrochloride salt. The import being these particular sets of salts would be considered the closest alternatives to one another. EX1002, ¶151. Thus, the combined teachings of WO '498 and Bastin would motivate the POSA to use the following list of three salts as alternatives to the hydrochloride salt exemplified in WO '498: hydrobromide, sulfate, and phosphate. *In re Fout*, 675 F.2d at 301 ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious.").

Having arrived at these three (3) alternative "[p]articularly preferred" acid salts, phosphoric acid salt would have been obvious. *Pfizer*, 480 F.3d at 1363 ("Taken together, these references provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge **to a few,** including benzene sulphonate.") (emphasis added); *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1344 (Fed. Cir. 2019) ("In *Pfizer*, the realm of possible anions could be reduced to a **manageable number** based on known properties of the anions, thus providing a POSA with a reasonable expectation of success.") (emphasis added); *Mylan Pharmaceuticals Inc.*, IPR2016-00510, Paper No. 45 at 47 (explaining that

Pfizer dealt with a situation where "the prior art there disclosed the base compound and a number of its salt forms."); EX1002, ¶152.

Indeed, *Pfizer* dealt with seven (7) alternative salts and found the claims obvious whereas the instant case deals with just three (3) alternative salts further evidencing the obviousness of the claim. *Pfizer*, 480 F.3d at 1364 ("Dr. Wells readily compiled a **list of seven alternative anions** — including the besylate — each of which he expected would form an amlodipine acid addition salt.") (emphasis added). Moreover, the combined teachings would have given a reasonable expectation of success. EX1002, ¶152; *Pfizer*, 480 F.3d at 1363, 1368; *Grunenthal GMBH*, 919 F.3d at 1344; *Mylan*, IPR2016-00510, Paper No. 45 at 47.

At the very least, it would be obvious to try in that the three alternative salts are a finite and identified set and their use would have been predictable providing a reasonable expectation of success. EX1002, ¶153. Neither WO '498 nor Bastin discourage using any of the "[p]articularly preferred" acid salts, and given this limited set and the relative ease with which the POSA would have been able to make the other three acid salts, the POSA would have found it obvious to try. *Bayer Schering Pharma AG v. Barr Laboratories*, 575 F.3d 1341, 1347-1348 (Fed. Cir. 2008) (explaining "obvious to try" jurisprudence); *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1071 (Fed. Cir. 2012) ("Where a skilled artisan

merely pursues 'known options' from 'a finite number of identified, predictable solutions,' the resulting invention is obvious under Section 103.").

As for making the phosphoric acid salt, it would have been a matter of routine experimentation for a POSA to synthesize alternative salt forms of the 33 compounds based on the preferred salts taught by WO '498 and the synthetic protocols disclosed therein. EX1002, ¶153; *Aller*, 220 F.2d at 456-57. Therefore, Claim 1 would have been obvious.

b) Claims 2 and 3

Claims 2 and 3 recite the same compound of Claim 1 but additionally recite the stereochemistry, i.e., the (R) and (S) configurations of sitagliptin, respectively. (R)-sitagliptin phosphate would have been obvious for the reasons discussed above as well as the fact that all 33 compounds of WO '498 (including sitagliptin) are in the (R) configuration. *See* EX1002, ¶155; EX1004, 46:1-26.

WO '498 also taught that there are only two configurations (i.e., (R) and (S)) and how to synthesize each. EX1004, 8:21-22, 24-27, 9:24-26, 11:11-14. Thus, a POSA would have known that only the (R) and (S) configurations are possible due to the asymmetric center at the beta carbon of sitagliptin phosphate, and how to synthesize and purify them. EX1002, ¶156. Accordingly, Claims 2 and 3 would have been obvious.

c) Claims 17 and 19

The analysis for Claims 17 and 19 is provided above in Grounds 1 and 3 and is incorporated by reference. In the interest of brevity, it is not repeated here but Petitioner provides a claim chart showing the relevant teachings:

17. A pharmaceutical composition comprising	EX1004, Claim 16; 3:26-27; 11:26-29; 12:10-12.
a therapeutically effective amount of the salt according to claim 2	EX1004, Claims 19-33, 11:32-35, 13:21-33; *see also* analysis for Claim 2.
in association with one or more pharmaceutically acceptable carriers	EX1004, 12:10-12, 20:10-16; 20:21-23.
19. A method for the treatment of type 2 diabetes comprising	EX1004, 3:24-26, 13:28-30.
administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.	EX1004, Claims 19-33, 11:32-35, 13:21-33.

EX1002, ¶158.

Given WO '498 teaches its compounds "are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes" and administering them in "a therapeutically effective amount," the skilled artisan would have had a reasonable expectation of success. EX1002, ¶159; EX1004, 3:24-26, 11:32-35, 13:21-33. Accordingly, Claims 17 and 19 would have been obvious.

d) Claims 21-23

The analysis for Claims 21 through 23 is provided above in Grounds 1 and 3 and is incorporated by reference. In the interests of brevity, it is not repeated here but Petitioner provides a claim chart showing the relevant teachings:

21. A process for preparing the salt of claim 2 comprising the step of contacting one equivalent of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine	Example 7 of WO '498 step A teaches the preparation of free base sitagliptin. Example 7, step B teaches that the salt form is then prepared in accordance with Example 1, step D—the pyrazine compound is reacted with a salt; *i.e.*, hydrogen chloride. EX1004, Example 7.
in an organic solvent or aqueous organic solvent	EX1004, 38:19 ("methanol").
with about a one equivalent of phosphoric acid	*See* discussion below.
at a temperature in the range of about 25-100° C.	EX1004, 38:20 ("ambient temperature," *i.e.*, room temperature or about 25 ˚C).
22. The process of claim 21 wherein said organic solvent is a C1-C5 linear or branched alkanol.	EX1004, 38:19 ("methanol," *i.e.*, C_1 alcohol).
23. The phosphoric acid salt of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine prepared according to the process of claim 21.	*See* analysis for Claim 2 and analysis at Ground 3, Claim 23.

EX1002, ¶161.

As Dr. Chorghade explains, it would have been obvious to a POSA to substitute the hydrogen chloride for a phosphoric acid, using the process of Example 7 of WO '498, to arrive at the 1:1 sitagliptin phosphate salt. From Example 7, a

POSA would have known that this reaction necessarily involves contacting the sitagliptin base molecule with the acid molecule, in order to form the salt. See discussion *supra* at Ground 1, Claim 21; EX1002, ¶162. Therefore, the skilled artisan would have had a reasonable expectation of success, and Claims 21-23 would have been obvious.

E. Ground 5: Claim 4 Would Have Been Obvious in View of WO '498, Bastin and Brittain

1. The Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the art has been described above. *Supra* at VIII.

2. The Scope and Content of the Prior Art

a) WO '498 (EX1004) and Bastin (EX1006)

WO '498 and Bastin are described above. *Supra* at X.A.1 & X.C.2.

b) Brittain (EX1005)

Brittain, "Polymorphism in Pharmaceutical Solids," was published in 1999 ("Brittain"). Brittain is prior art to the '708 patent under 35 U.S.C. § 102(b). Brittain was not disclosed to the Examiner or cited by the Examiner during prosecution of the application which issued as the '708 patent. Brittain discusses the prevalence of crystal hydrates of pharmaceutical substances. *Id*. at 126-129. As Brittain teaches:

> Focusing on active drug substances, it is estimate that approximately one-third of the pharmaceutical actives are capable of forming crystalline hydrates [3]. A search of the Cambridge Structural Database (CSD) shows that

> approximately 11% of all reported structures contain molecular water [4]. This represents over 16,000 compounds. If organometallics are excluded, this number drops to approximately 6,000 (3.8%), and the breakdown of these according to hydration number is shown in Fig. 1. **This shows the expected trend in which monohydrates are most frequently encountered**, and where the frequency decreases almost exponentially as the hydrate number increases.

Ex. 1005 at 128 (emphasis added). Figure 1 of Brittain showing the prevalence of crystalline monohydrates over other crystalline hydrates is reproduced below:

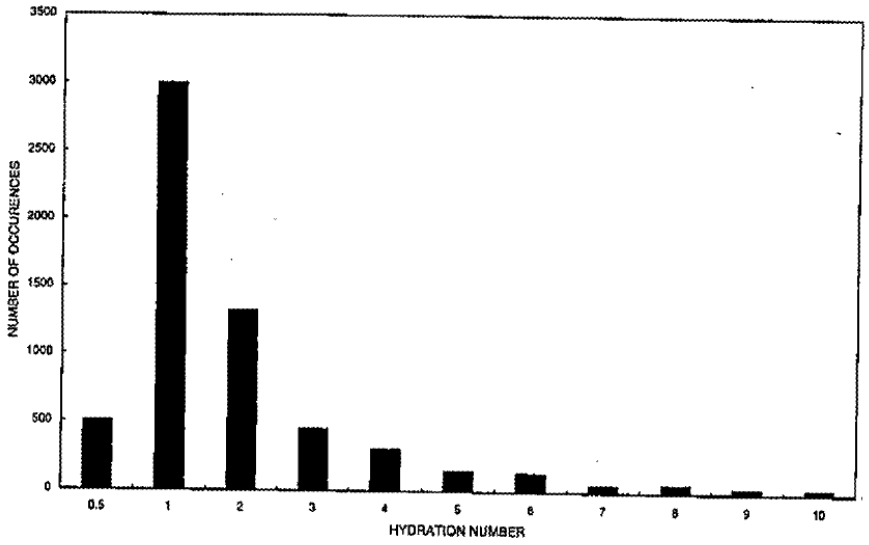

Fig. 1 Occurrence of various crystalline hydrate stoichiometries.

3. The Differences Between the Claim and Prior Art

Claim 4 recites "[t]he salt of claim 2 characterized in being a crystalline monohydrate." As explained in Ground 4, Claim 2's (R)-sitagliptin phosphate would have been obvious over WO '498 and Bastin. *Supra*.

WO '498 also discloses that its "[s]alts in the solid form may exist in more than one **crystal** structure, **and may also be in the form of hydrates**." EX1004, 9:32-34 (emphasis added); EX1002, ¶169. Thus, the POSA also would have expected that (R)-sitagliptin phosphate of Claim 2 exists as a crystalline hydrate. *Id.*; *Google Inc. v. Jongerius Panoramic Techs, LLC*, IPR2013-00191, Paper 70 at 37 (P.T.A.B. Aug. 12, 2014) (explaining that in an IPR, prior art references are presumed to be enabled).

Brittain teaches that of the crystalline hydrates of pharmaceutical substances, not only are the crystalline monohydrates expected to be the most "frequently encountered" (EX1005 at 128), an empirical analysis shows that to be a fact. *Id*. at Fig. 1. In fact, from inspection of Figure 1, Dr. Chorghade opines that the sum of all the other crystalline hydrates would be lower than the number of monohydrate crystalline hydrates. EX1002, ¶170.

Therefore, given that WO '498 discloses that the hydrates exist of the compounds disclosed therein, the "most frequently encountered" hydrate, i.e., the monohydrate, would have been obvious to a POSA. EX1002, ¶170; EX1005, 128.

Moreover, the skilled artisan would have had reasonable expectation of success given the "expected trend" is that the monohydrate is the "most frequently encountered." *Id*. Therefore, Claim 4 would have been obvious.

A. Ground 6: Claim 4 Would Have Been Obvious in View of WO '498 and Brittain

1. The Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the art has been described above. *Supra* at VIII.

2. The Scope and Content of the Prior Art

a) WO '498 (EX1004) and Brittain (EX1005)

WO '498 and Brittain have been described above. *Supra* at X.A.1 & X.E.b.

3. The Differences Between the Claim and Prior Art

The text of Claim 4 recites "[t]he salt of claim 2 characterized in being a crystalline monohydrate." As explained in Ground 1, WO '498 anticipates Claim 2. Upon making the predicate finding that Claim 2 is anticipated by WO '498, then it follows that (R)-sitagliptin phosphate is necessarily a prior art compound, and then Claim 4 of '708 patent would have been obvious in view of WO '498 and Brittain. As explained above, the '708 patent admits that at least sitagliptin and its "pharmaceutically acceptable salts" are in the prior art. EX1001, 1:49-57; *One World Technologies Inc.*, IPR2017-00126, Paper 67 at 14-15.

WO '498 also discloses that its "[s]alts in the solid form may exist in more than one crystal structure, **and may also be in the form of hydrates**." EX1004 at

9:32-34 (emphasis added). Thus, the POSA also would have expected that (R)-sitagliptin phosphate of Claim 2 exists as a hydrate. EX1002, ¶174. Brittain teaches that of the crystalline hydrates of pharmaceutical substances, not only are the monohydrates expected to be the most "frequently encountered" (EX1005 at 128), an empirical analysis shows that to be a fact. *Id*., Fig. 1. Therefore, given that WO '498 discloses that the hydrates exist of the compounds disclosed therein, the "most frequently encountered" hydrate, i.e., the monohydrate, would have been obvious to a POSA. EX1002, ¶176; EX1005, 128. Moreover, the skilled artisan would have had reasonable expectation of success given the "expected trend" is that the monohydrate is the "most frequently encountered." EX1002, ¶176; EX1005, 128. Therefore, Claim 4 would have been obvious.

B. Secondary Considerations of Nonobviousness

Secondary considerations have no relevance to the anticipation inquiry, only to the obviousness inquiry. *Cohesive Techs., Inc. v. Waters Corp*., 543 F.3d 1351,1364 (Fed. Cir. 2008). While secondary considerations of nonobviousness must be taken into account in an obviousness determination, they do not necessarily control. *Newell Cos., Inc. v. Kenney Mfg. Co*., 864 F.2d 757, 768 (Fed. Cir. 1988). A strong case of obviousness cannot be overcome by secondary considerations of nonobviousness. *Pfizer*, 480 F.3d at 1372. To the extent Patent Owner does assert any secondary considerations, including alleged unexpected results, detailed

consideration of Patent Owner's evidence should not be undertaken until Petitioner has had an opportunity to respond to it. *Amneal Pharmaceuticals, LLC v. Supernus Pharmaceuticals, Inc*., IPR2013-00368, Paper 8 at 12-13 (P.T.A.B. Dec. 2013); *Koios Pharms. LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, IPR2016-01370, Paper 13 at 35 (P.T.A.B. Feb. 8, 2017); *Quanergy Systems, Inc. v. Velodyne Lidar, Inc.*, IPR2018-00256, Paper 14 at 11 (P.T.A.B. May 25, 2018).[25]

That said, no other objective indicia of nonobviousness was presented or discussed during prosecution. To the extent the specification contends there are alleged unexpected results (EX1001, 2:9-15, 4:24-26), such evidence is flawed. Other than the unsupported statements in the specification, no data is presented supporting these claims. EX1002, ¶179. Indeed, any allegation of improvements to properties in the Specification such as "physical and chemical stability, such as stability to stress, high temperatures and humidity, as well as improved physicochemical properties, such as solubility and rate of solution," lack a nexus to

[25] A showing of "copying in the ANDA context where a showing of bioequivalence is required for FDA approval" is not compelling evidence of nonobviousness. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc*., 377 F. App'x 978, 983 (Fed. Cir. 2010). Thus, any argument by Patent Owner that ANDA submissions suggest nonobviousness because of copying is without merit.

the claims in that the challenged claims do not recite any limitations addressed to the alleged improvements. EX1002, ¶181; *Amneal Pharms. LLC v. Hospira, Inc*., IPR2016-01577, Paper 11 at 13 (P.T.A.B. at Feb. 9, 2017) ("Stability over prolonged periods of time, however, is not a limitation in any of the challenged claims."); *Dr. Falk Pharma GmbH v. GeneriCo, LLC*, No. 2017-2312, 2019 WL 2452362, at *8 (Fed. Cir. June 12, 2019).

Significantly, the specification of the '708 patent does not even consider these alleged results as "unexpected results" but rather characterizes them as mere "improve[ments]" over the prior art. EX1002, ¶180. An improvement is a difference in degree, not in kind, and is not probative of obviousness. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005); *In re Williams*, 36 F.2d 436, 438 (C.C.P.A. 1929) ("[a] change of form . . . or the substitution of equivalents doing the same thing as the original invention. . . is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions.").

Moreover, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc*., 441 F.3d 963, 970 (Fed. Cir. 2006); *Modernatx Inc. v. Curevac AG*, IPR2017-02194, Paper 45 at 74 (P.T.A.B. April 16,

2019). The specification has no such comparison. *Modernatx Inc.*, IPR2017-02194, Paper 45 at 75 ("Again, we do not find this evidence persuasive of 'unexpected results' because we cannot determine whether Dr. Thran compared the results to the closest prior art.").

Finally, Petitioner notes that any objective indicia Patent Owner can present to the '708 patent would be undercut by the fact that the FDA Orange Book includes entries for Janumet® and Januvia® and multiple other patents. EX1008 & EX1009; *Acorda Therapeutics Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310, 1337-1342 (Fed. Cir. 2018).

XI. THE BOARD SHOULD INSTITUTE TRIAL BASED ON MYLAN'S PETITION (35 U.S.C. § 325(D) OR § 314(A))

The Board should not exercise its discretion pursuant to 35 U.S.C. § 325(d) to deny institution of Mylan's Petition. As discussed above, the Examiner raised no prior art rejections. Thus, the arguments presented in this Petition are necessarily different from those relied upon during prosecution and are not cumulative of the prior art evaluated during examination. *Becton, Dickinson and Company v. B. Braun Melsungen AG*, IPR2017-01586, slip op. at 17-18 (P.T.A.B. Dec. 15, 2017) (Paper 8) (precedential) (factors (a), (b), and (d)).

Moreover, even if any of the references cited in this Petition were disclosed to the Examiner, "the Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference

was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharmaceuticals Inc*., IPR2019-00740, Paper 15 at 65 (P.T.A.B. Aug. 20, 2019) (citing cases). Therefore, even if some of the references relied upon in this Petition were cited during examination (but not used by the Examiner), Petitioner respectfully asks the Board to decline using its discretion under Section 325(d). *Id*.

Turning to Section 314(a), to the best of Petitioner's knowledge, this is the first IPR directed to the '708 patent. *See generally Valve Corp. v. Elec. Scripting Prods., Inc*., IPR2019-00062, -00063, -00084, Paper 11 (P.T.A.B. Apr. 2, 2019) (precedential) (discussing the prejudice to Patent Owner by subjecting it to multiple petitions); *Mylan Pharmaceuticals Inc. v. Sanofi-Aventis Deutschland GMBH*, IPR2018-01680, Paper 22 at 17 (P.T.A.B. Apr. 3, 2019) ("the *General Plastics* factors were articulated in the context of follow-on petitions."). Furthermore, the corresponding district court proceeding is still in its infant stages. Thus, Petitioner has not gained any tactical advantage by making the Patent Owner substantively participate in the underlying district court litigation only then to use such information to the detriment of Patent Owner. *NHK Spring Co., Ltd. v. Intri-Plex Techs., Inc*., Case IPR2018-00752, Paper 8 at 19-20 (P.T.A.B. Sept. 12, 2018) (precedential).[26]

[26] Even if Patent Owner could allege that some information has been exchanged, the inquiry under Section 314(a) is whether the parties remain on equal footing. *Kashiv*

Finally, Patent Owner, citing *NHK Spring*, may focus its Section 314(a) arguments by comparing the trial date and the expected date of the PTAB Final Written Decision. As the PTAB has noted, even if "the facts in *NHK Spring* and the circumstances of this case may seem similar," wrapping a Section 314(a) analysis with a singular focus on the District Court's schedule ignores "the uncertainty associated with litigation schedules." *Mylan*, IPR2018-01680 at 16-17, fn. 6 (declining to exercise Section 314(a) discretion based on a consideration of the district court schedule). Indeed, illustrating the dangers of myopically focusing on the district court trial schedule, the *Mylan* panel noted that in the very case underlying *NHK Spring*, the district court did ultimately move back the trial date six months. *Mylan*, IPR2018-01680 at fn. 6.

Likewise, other panels have also refused to read *NHK Spring* as standing for the proposition that the only relevant inquiry is a focus on the potential trial date. As the *Sandoz* panel noted, in *NHK Spring*, the Board denied institution under 35 U.S.C. § 325(d) because the arguments advanced in the petition were

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Biosciences, LLC v. Amgen Inc., IPR2019-00791, Paper 15 at 32 (P.T.A.B. Sept. 11, 2019). Furthermore, activities that occur after filing of a petition have no bearing on Section 314(a). *Kashiv*, IPR2019-00791 at 32; *Apotex Inc. v. UCB Biopharma SPRL*, IPR2019-00400, Paper 17 at 34 (P.T.A.B. July 15, 2019).

substantially similar to those made before the Examiner *and then* considered the "advanced state of the district court proceeding as an additional factor that weighed in favor of denying the petition." *Sandoz Inc. v. Pharmacylics LLC*, IPR2019-00865, Paper 8 at 11 (P.T.A.B. Sept. 26, 2019). As mentioned above, Patent Owner cannot advance any credible Section 325(d) arguments. *Amgen*, IPR2019-00740 at 65.

Therefore, Petitioner respectfully asks the Board to decline using its discretion under Section 314(a).

XII. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that Claims 1-4, 17, 19, and 21-23 of the '708 patent are unpatentable over the prior art cited herein and respectfully requests that the Board so find.

RESPECTFULLY SUBMITTED,

Katten Muchin Rosenman LLP

Date: October 30, 2019

/ Jitendra Malik /

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the argument section of this Petition (Sections I-III, V-XII) has a total of 13,534 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

Katten Muchin Rosenman LLP

By: / Jitendra Malik /
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CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4), and 42.105, the undersigned certifies that on October 30, 2019, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,326,708, Power of Attorney, Exhibit List, and all supporting exhibits were served via Express Mail to the Patent Owner by serving the correspondence address of record for the '708 patent:

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Courtesy copies of the foregoing Petition, Power of Attorney, Exhibit List, and all supporting exhibits were also served via Express Mail to the following:

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