Paper No. 1

Filed: September 24, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HIKMA PHARMACEUTICALS USA INC.,
Petitioner,

v.

SK BIOPHARMACEUTICALS CO., LTD., and AXSOME MALTA LTD,
Patent Owners.

IPR2024-01418
U.S. Patent No. 11,560,354

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,560,354

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 11,560,354
1002	U.S. Patent No. 11,560,354 File History
1003	Declaration of Dr. Salvatore Lepore, Ph.D.
1004	CV of Dr. Salvatore Lepore, Ph.D.
1005	US Pub. No. 2009/0312416 ("Ahnaou")
1006	US 2005/0080268 ("Choi268")
1007	S. Kim, *Pharmaceutical Industry Practices on Genotoxic Impurities*, Chapter 14 "Salt Formation of Pharmaceutical Compounds and Associated Genotoxic Risks" 385–426 (Kim Lee ed., CRC Press 2015) ("Kim")
1008	C.G. Fraga, *Profiling of Volatile Impurities in Tetramethylenedisulfote tramine (TETS) for Synthetic-Route Determination* 210 FORENSIC SCI. INT'L 164 (2011) ("Fraga")
1009	Z. Sobol, *Genotoxicity Profiles of Common Alkyl Halides and Esters with Alkylating Activity* 633 MUTUAT RES. 80 (2007) ("Sobol")
1010	Wayback Machine webpage – T. Kaleemullah et al., *Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride* 3(6) DER PHARM. CHEMICA 390 (2011) (https://web.archive.org/web/20160203013049/http://derpharmachemica.com/vol3-iss6/DPC-2011-3-6-390-399.pdf) (captured September 19, 2024)
1011	Declaration of Dr. Sylvia Hall-Ellis certifying the publication date of Ex. 1016
1012	Unichem Dismissal, Docket No. 103, June 14, 2024
1013	Stipulated Consolidation and Scheduling Order, Docket No. 110, September 24, 2024

1014	David Liu et al., *Recent Advances in Trace Analysis of Pharmaceutical Genotoxic Impurities* 51 J. PHARM. BIOMED. ANALYSIS 999 (2010) ("Liu")
1015	Zadeo Cimarosti et al., *Application of Quality by Design Principles to Support Development of a Control Strategy for the Control of Genotoxic Impurities in the Manufacturing Process of a Drug Substance* 14 ORGANIC PROCESS RSCH. & DEV. 993 (2010) ("Cimarosti")
1016	T. Kaleemullah et al., *Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in Ziprasidone Hydrochloride* 3(6) DER PHARM. CHEMICA 390 (2011) ("Kaleemullah")
1017	Courtney M. Callis et al., *Risk Assessment of Genotoxic Impurities in Marketed Compounds Administered Over a Short-Term Duration: Applications to Oncology Products and Implications for Impurity Control Limits 14*(4) ORGANIC PROCESS RSCH. & DEV. 986 (2010) ("Callis")
1018	*Guideline on the Limits of Genotoxic Impurities*, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (Jun. 28, 2006) ("CHMP")
1019	Q. Yang et al., *Controlling the Genotoxins Ethyl Chloride and Methyl Chloride Formed During the Preparation of Amine Hydrochloride Salts from Solutions of Ethanol and Methanol* 13 ORGANIC PROCESS RSCH. & DEV. 786 (2009) ("Yang")

I. INTRODUCTION

Petitioner (Hikma Pharmaceuticals USA Inc.) submits this Petition for *Inter Partes* Review of claims 1-8 of U.S. Patent No. 11,560,354 (the "354 Patent" (Ex. 1001)), assigned to Patent Owners. Petitioner submits that the Challenged Claims of the 354 Patent are unpatentable under 35 U.S.C. §103 in view of the references discussed herein.

II. MANDATORY NOTICES

A. Real Party-in-Interest

The real party-in-interest for this Petition is Hikma Pharmaceuticals Inc.

B. Related Matters

The 354 Patent is asserted by Patent Owners in Civil Action No. 23 CV 20354 (MCA)(LDW) (consolidated) in the United States District Court District of New Jersey. The co-defendants in the Civil Action are Alkem Laboratories Ltd., Aurobindo Pharma USA, Inc., Hetero USA Inc., Hetero Labs Limited Unit-V, and Hetero Labs Ltd.[1] The other patents asserted in the Civil Action are U.S. Patent Nos. 8,440,715 ("the '715 Patent"), 10,195,151 ("the '151 Patent"), 10,512,609 ("the '609 Patent"), 11,439,597 ("the '597 Patent"), 10,912,754 ("the '754 Patent"), 10,959,976

[1] Defendants Unichem Laboratories Ltd. and Sandoz Inc. settled and were subsequently dismissed from the Civil Action.

("the '976 Patent"), 11,160,779 ("the '779 Patent"), 10,940,133 ("the '133 Patent"), 11,648,232 ("the '232 Patent"), 11,771,666 ("the '666 Patent"), 11,771,667 ("the '667 Patent"), 11,779,554 ("the '554 Patent"), 11,793,776 ("the '776 Patent"), 11,839,598 ("the '598 Patent"), 11,839,599 ("the '599 Patent"), 11,850,226 ("the '226 Patent"), 11,850,227 ("the '227 Patent"), 11,850,228 ("the '228 Patent"), 11,857,528 ("the '528 Patent"), 11,865,098 ("the '098 Patent"), 11,872,203 ("the '203 Patent"), 11,872,204 ("the '204 Patent"), 11,998,639 ("the '639 Patent"), 11,969,404 ("the '404 Patent"), 11,986,454 ("the '454 Patent"), 11,986,455 ("the '455 Patent"), 12,005,036 ("the '036 Patent"), 12,036,194 ("the '194 Patent"), and 12,064,411 ("the '411 Patent") (collectively, the "Asserted Patents")[2].

[2] U.S. Patent Nos. 8,877,806, 9,604,917, 10,351,517, and 11,753,368 were asserted only against Unichem Laboratories Ltd., which has entered a stipulation dismissing it from this litigation. *See* Ex. 1012.

C. Lead and Back-Up Counsel and Service

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Petitioner consents to electronic service by email at HikmaSol@winston.com and the e-mail addresses listed above.

III. PAYMENT OF FEES

Petitioner authorizes the Office to charge the filing fee and any other necessary fee to Deposit Account No. 501814.

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW

A. Grounds for Standing

Petitioner certifies that the 354 Patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review challenging the claims on the identified ground herein. Petitioner has not filed a civil action challenging the validity of a claim of the 354 Patent. This petition is being filed no more than 1 year after the date on which Petitioner was served with a complaint alleging infringement of the 354 Patent.

B. Identification of Challenged Claims

Ground 1: Claims 1-8 are unpatentable as obvious under 35 U.S.C. §103 based on Choi268 (Ex. 1006) in view of Kaleemullah (Ex. 1016) in further view of Ahnaou (Ex. 1005).

V. THE 354 PATENT

A. Effective Filing Date

Petitioner assumes for the purposes of this Petition that **September 6, 2016,** is the effective filing date.

B. Person of Ordinary Skill in the Art

A Person of Ordinary Skill in the Art ("POSITA") in September 2016 would have had a working knowledge of pharmacology and organic chemistry art that is pertinent to the 354 Patent. A POSITA would have had a Ph.D. in a field such as chemistry, biochemistry, medicinal chemistry, organic chemistry, analytical

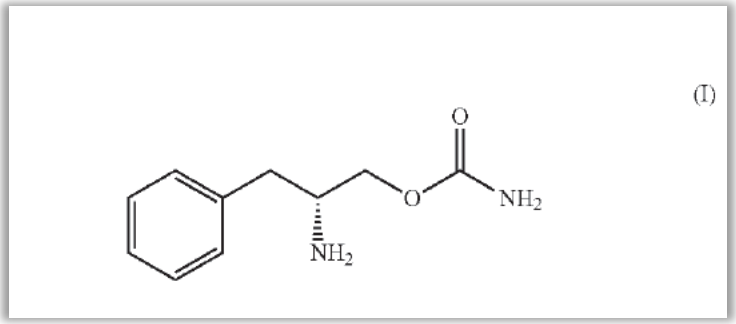
chemistry, pharmaceutical chemistry, pharmaceutics, or the like. Alternatively, a POSITA would have had an M.S. or Bachelor's Degree and several years of relevant experience in the research, development, and characterization of a pharmaceutical compound or an organic compound. Ex. 1003, ¶28.

C. Overview of the 354 Patent

The 354 patent issued on January 24, 2023, and claims priority to U.S. Provisional Application No. 62/383,822 ("the '822 provisional application"), filed on September 6, 2016. 354 Patent, 1:12–15. Because the '822 provisional application was filed after March 16, 2013, the '354 patent is subject to the provisions of the AIA.

The 354 Patent is generally directed to (R)-2-amino-3-phenylpropyl carbamate (APC) (see formula 1 below) in its hydrochloride salt form: "(R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride,[3] a method of preparing APC hydrochloride, and methods of using the same to treat disorders." Ex. 1001, Abstract.

[3] "(R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride," "O-Carbamoyl-(D)-phenylalaninol hydrochloride," "solriamfetol hydrochloride," and "solriamfetol HCl" all refer to the same compound. As such, these terms are used interchangeably herein.



Ex. 1001, 4:40-50.

Initially, while the 354 Patent describes that 2-CP may be generated during the solriamfetol HCl manufacturing process, it contains no guidance on how to achieve a level "*less than about 5 ppm*" and "*less than about 1 ppm*" as required in claims 1 and 2. Ex. 1003, ¶¶37–43.

Additionally, while the 354 Patent mentions achieving zero and non-zero 2-CP levels in multiple passages, there is no description of a technique to determine such levels, *e.g.*, the 354 Patent does not specify any limits of detection (LOD). Ex. 1003, ¶¶42–43. The 354 Patent further discloses that in two additional batches made with the same process, "2-CP levels in the product were less than 1 ppm." Ex. 1001, 12:17–19. "Less than" 1 ppm includes zero, and again there appears to be no positive indication that there was any 2-CP at all in the two batches described in the 354 Patent. Ex. 1001, 12:17–19.

VI. CLAIM CONSTRUCTION

Claims are given their "ordinary and customary meaning" as understood by a POSITA and the prosecution history pertaining to the patent. 37 C.F.R. §42.100(b).

Because a POSITA would find the challenged claims unpatentable under any interpretation consistent with their plain and ordinary meaning in the context of the 354 Patent, the Board need not expressly construe the claim terms. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

VII. PRINCIPAL PRIOR ART

A. Summary of Choi268

U.S. Patent Publication No. 2005/0080268 to Choi et al. (Ex. 1006) was filed on October 3, 2003, and published on April 14, 2005, and, therefore, qualifies as prior art to the 354 Patent under 35 U.S.C. §102(a)(1), with no exceptions available under 35 U.S.C. §102(b)(1).

Choi268 is generally directed to a method of preparing solriamfetol HCl using HCl and isopropanol, illustrated in Example 1. *See* Ex. 1006, [0068]–[0069]. Specifically, Choi268 discloses the preparation of Preparation of O-Carbamoyl-(D)-phenylalaninol free base (i.e., solriamfetol), as well as the hydrochloride salt form. Ex. 1003, ¶¶48–50.

B. Summary of Kaleemullah

Kaleemullah is prior art under 35 U.S.C. §102(a)(1), with no exceptions available under 35 U.S.C. §102(b)(1) because it is a printed publication that was publicly accessible to the interested public at least as of January 31, 2011. *See* Ex. 1011, 36. In addition, Kaleemullah was also captured by the Wayback Machine as

early as February 3, 2016 (*see* Ex. 1010), so it was therefore a prior art printed publication §102(a)(1) that was publicly accessible as of that date as well. *See* MPEP §2128(II)(E) ("Prior art obtained via the Wayback Machine sets forth a prima facie case that the art was publicly accessible at the date and time provided in the time stamp."); *Valve Corp. v. Ironburg Inventions Ltd*., 8 F.4th 1364, 1374–75 (Fed. Cir. 2021) ("District courts have taken judicial notice of the contents of webpages available through the Wayback Machine 'as facts that can be accurately and readily determined from sources whose accuracy cannot reasonably be questioned.'" (quoting *Erickson v. Neb. Mach. Co*., No. 15-CV-01147-JD, 2015 WL 4089849, at *1 n.1 (N.D. Cal. July 6, 2015))).

Kaleemullah discloses an analytical technique to detect isopropyl chloride present in a drug substance, ziprasidone hydrochloride. Ex. 1016, Abstract. The analytical technique developed in Kaleemullah is a headspace gas chromatographic (GC) method with a flame ionization detector. Ex. 1016, 391.

Kaleemullah teaches a method to detect isopropyl chloride (2-CP) that may be produced when a drug containing an amine base moiety "is treated with hydrochloric acid leading to a precipitate" as a hydrochloride salt. Ex. 1016, 391.

Kaleemullah discloses that its method is capable of detecting 2-CP at levels as low as 0.93 ppm. Ex. 1016, 395 and Table 2. Kaleemullah explains "methyl chloride, ethyl chloride and isopropyl chloride are reported as carcinogen and methyl

chloride as teratogen. Therefore, it is necessary that, these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC)." Ex. 1016, 391. For example, Kaleemullah states that its estimated TTC value was "1.5µg/person/day intake of a genotoxic impurity." Ex. 1016, 391. Kaleemullah explains that 1.5µg/person/day intake of a genotoxic impurity as "an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006] as well as risk assessment literature." Ex. 1016, 391. Ex. 1003, ¶¶51–54.

C. Summary of Ahnaou

U.S. Publication No. 2009/0312416 to Ahnaou et al. (Ex.1005) was filed as International Application No. PCT/US06/22407, published as WO 2006133393, and subsequently published on December 17, 2009 as U.S. Pub. No. 2009/0312416, and qualifies as prior art to the 354 Patent under 35 U.S.C. §102(a)(1), with no exceptions available under 35 U.S.C. §102(b)(1).

Ahnaou is generally directed to a method of treating Excessive Daytime Sleepiness (EDS) where a "method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of Formula Ib (R)-(beta-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-amino-

benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates." Ex. 1005, [0028]; *see also* [0029]; Ex. 1003, ¶¶55–59.

VIII. CLAIMS 1-8 ARE UNPATENTABLE

A. Ground 1: Choi268, Kaleemullah, and Ahnaou render obvious claims 1-8

1. The Combination of Choi268, Kaleemullah, and Ahnaou

Choi268 does not expressly disclose the formation of "*2-chloropropane*" ("2-CP") during the synthesis of solriamfetol hydrochloride (using both HCl and isopropanol as reagents during salt precipitation). However, a POSITA would have recognized that based on Choi268's method of preparation, "*2-chloropropane*" (alternatively isopropyl chloride) would be formed, in view of Kaleemullah's disclosure that treating ziprasidone base "in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid" results in the formation of "[i]sopropyl chloride." Thus, Kaleemullah's express disclosure of the formation of "*2-chloropropane*" during salt precipitation with HCl and isopropanol would inform a POSITA that "*2-chloropropane*" would be formed in Choi268's method of preparing solriamfetol hydrochloride. Ex. 1003, ¶60.

Choi268 and Kaleemullah are analogous art to the 354 Patent because each is in the field of pharmaceutical chemistry. Indeed, similar to the 354 Patent, Choi268 discloses methods of preparing solriamfetol hydrochloride, and more specifically, salt precipitation with HCl and isopropanol. Kaleemullah teaches that such use of

precipitation treatment to synthesize a hydrochloric salt form of an active ingredient can result in the formation of 2-CP—the same impurity that the 354 Patent claims are directed to. In short, both Choi268 and Kaleemullah are applicable to drug substances, and are thus analogous art to the 354 Patent. Ex.1006, [0001]–[0002], [0069]; Ex. 1016, Abstract and 390–91. Moreover, both Choi268 and Kaleemullah teach use of HCl and isopropanol to form the hydrochloric salt of an active ingredient. Specifically, Choi268 discloses preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride by dissolving O-Carbamoyl-(D)-phenylalaninol in isopropanol and charging the resulting mixture with "HCl solution in isopropanol." Ex. 1006, [0069]. Kaleemullah teaches a method for detecting "residual" amounts of isopropyl chloride (2-CP) that may be produced when a drug containing an amine base moiety "is treated with hydrochloric acid leading to [a] precipitate" of the hydrochloride salt form. Ex. 1016, 391. For example, Kaleemullah describes that as a result of treating ziprasidone base "in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid," "[i]sopropyl chloride may form at the salt formation step." Ex. 1016, 391. Moreover, similar to Kaleemullah's ziprasidone, Choi268's solriamfetol possesses a basic amine unit that can be converted to hydrochloride salt. Ex. 1003, ¶61.

Moreover, the teachings of Choi268 and Kaleemullah are reasonably pertinent to the purported problem that was solved by the inventors of the 354 Patent. In

particular, the 354 Patent states that the claimed invention "overcomes shortcomings in the art by providing . . . a method of preparing APC [solriamfetol] with minimal contaminants." Ex. 1001, 1:42–44. As discussed above, Choi268 provides a "novel process" for synthesizing solriamfetol hydrochloride. Ex. 1006, [0001]. Kaleemullah discloses that the salt precipitation process used in Choi268 can result in the formation of genotoxic impurities (e.g., 2-CP), which should be minimized, at the very least, to a "threshold of toxicological concern." Ex. 1006, 391. Accordingly, it would have been obvious to a POSITA that the process of synthesizing solriamfetol hydrochloride described in Choi268 as modified by Kaleemullah's teachings of the formation and detection of "*2-chloropropane*" addresses the problem of preparing a drug substance that has minimal impurities. Ex. 1003, ¶62.

Based on the teachings of Kaleemullah, Choi268's method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride for use in a pharmaceutical composition would be modified to additionally include Kaleemullah's teachings of a method of detecting 2-CP in Choi268's method of preparation of O-Carbamoyl-(D)-phenylalaninol hydrochloride. Ex. 1016, Table 2; *see also* Ex. 1016, 391–93 (describing details of Kaleemullah's method of detecting 2-CP). In particular, Kaleemullah discloses that its analytical method (a headspace gas chromatography technique), which is validated according to ICH guidelines, is capable of detecting

2-CP at levels as low as 0.93 ppm. Ex. 1016, Table 2 and 393. A POSITA would have been motivated to make the combination based the teachings of Kaleemullah since Kaleemullah is concerned with the levels of "*2-chloropropane*" that are formed during the salt precipitation process, and further emphasizes the importance controlling the levels of genotoxic impurities, including 2-CP. For example, Kaleemullah states that "methyl chloride, ethyl chloride and isopropyl chloride are reported as carcinogen and methyl chloride as teratogen. Therefore, it is necessary that, these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC)." Ex. 1016, 393. Kaleemullah further discloses that, as of the priority date, the estimated TTC value was "1.5µg/person/day intake of a genotoxic impurity," e.g., 2-CP. Ex. 1016, 391. Kaleemullah explains that a 1.5µg/person/day intake of a genotoxic impurity is "an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006] as well as risk assessment literature." Ex. 1016, 391. A POSITA would have understood that 1.5µg/day translates to 1.5ppm per day, assuming[4] a daily dose of 1.0g of the API.

[4] It was within the knowledge of a POSITA to assume a daily dose of 1.0g of API for conservatively determining genotoxic impurity (GTI) limits. *See* Ex. 1017, Table 2, footnote d.

Additionally, Callis, which reflects the knowledge of a POSITA, describes that the "daily chronic limit" of "isopropyl chloride" ("*2-chloropropane*") is "1.5ppm." Ex. 1017, Table 2. Ex. 1003, ¶63.

A POSITA would have recognized that Choi268's method of preparing a drug substance (e.g., O-Carbamoyl-(D)-phenylalaninol hydrochloride) would be modified to include a method of detecting 2-CP, and a POSITA would have been motivated to do so, based on other teachings in the prior art that reflect a POSITA's knowledge regarding the presence of genotoxic impurities (e.g., 2-CP) in drug substances, and the common concern to limit the daily intake of such impurities or otherwise reduce the level of such impurities in the composition of a drug substance. For example, Liu explains that "[g]enotoxic impurities (GTIs) in pharmaceuticals at trace levels are of increasing concerns to both pharmaceutical industries and regulatory agencies due to their potentials for human carcinogenesis. Determination of these impurities at ppm levels requires highly sensitive analytical methodologies … in pharmaceutical R&D." Ex. 1014, Abstract. As another example, Cimarosti recognizes the need for "developing and validating methods to measure trace levels of genotoxic impurities." Ex. 1015, 993. As yet another example, Kim, reflecting the knowledge of a POSITA, highlights its concern for reducing 2-CP levels to "trace amounts." Kim explains that "[e]ven small amounts of residual alcohol in API can, in principle, interact with a strong acid used in the downstream formulation process

to produce trace amounts of a genotoxin in the drug product." Ex. 1007, 422. Consistent with these teachings, a POSITA would have understood the increased concern to limit genotoxic impurities in drug substances. In addition, a POSITA would have understood the need to reduce genotoxin levels in drug substances to limits even lower than toxicology-based requirements (e.g., lower than 1.5µg/person/day) in view of the EMEA guidelines cited in Kaleemullah and which disclose the—"as low as reasonably practicable" (ALARP principle)—for genotoxic impurities (such as 2-CP). Ex. 1018, 5. Thus, the EMEA guidelines, reflect the POSITA's understanding that the levels of genotoxic impurities (such as 2-CP) in a drug substance should be limited as much as possible and provide the motivation to combine Choi268 and Kaleemullah such that the method of preparing solrimafetol hydrochloride, as described in Choi268 to additionally include Kaleemullah's teachings of method of detecting 2-CP in the solrimafetol hydrochloride drug substance prepared using Choi268's method. Furthermore, Callis, reflecting the knowledge of a POSITA, emphasizes the importance of the ALARP principle. "Consideration of the ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require." Ex. 1017, 986. "GTI control typically must be demonstrated at very low (ppm) levels in the API or synthetic intermediates." Ex. 1017, 986. As such, Callis teaches that, "[w]hen considering potential risk to the patient, genotoxic impurities must often be

controlled to much lower levels than required by the ICH Q3A(R2) guideline for non-GTIs." Ex. 1017, 990. These prior art references reflect the POSITA's understanding of the concern to reduce genotoxin levels in drug substances to limits even lower than toxicology-based requirements. Accordingly, a POSITA would be motivated to combine Choi268 and Kaleemullah for at least these reasons. Ex. 1003, ¶64.

Moreover, modifying Choi268's method to additionally include a method of detecting 2-CP, as taught in Kaleemullah, would be a simple substitution well within the skill of a POSITA because it would only entail adding an extra analytical step to Choi268's method. In particular, Kaleemullah's method is an analytical technique that uses headspace gas chromatography to detect 2-CP levels in a drug substance (*see* Ex. 1016, Abstract), and Choi268 describes a method of synthesizing a drug substance (*see* Ex. 1006, Abstract). For example, in Choi268's method, after the O-Carbamoyl-(D)-phenylalaninol hydrochloride product is "washed thoroughly with ice-chilled isopropanol-acetone and dried in vacuo" (Ex. 1006, [0069]), Kaleemullah's "gas chromatographic methods … for the quantitative determination of residual . . . Isopropyl chloride" (Ex. 1016, 391) can be implemented. A POSITA would recognize Table 1 of Kaleemullah teaches the gas chromatography conditions used in the proposed modification. Indeed, Choi268 contemplates "modifications in the practice of [its] invention." Ex. 1006, [0077]. Choi268 states that the

modifications "can be readily made by, those skilled in the art without departing from the scope of the invention described above." Ex. 1006, [0077]. "Those skilled in the art will recognize that the invention covers all alternatives, modifications and equivalents as may be included within the scope of the appended claims." Ex. 1006, [0067]. Therefore, a POSITA would have understood that modifying Choi268's method of preparing the drug substance to additionally Kaleemullah's teachings of an analytical technique would not render Choi268's method inoperative for its intended purpose. In fact, including Kaleemullah's method of detecting 2-CP in Choi268's method of preparing the drug substance would allow detection of impurities in the final drug substance, thereby leading to an improvement—a resulting drug substance with minimal impurities. Ex. 1003, ¶65.

Although Kaleemullah discloses use of its analytical method in connection with an exemplary drug ziprasidone hydrochloride, its method has wider applicability to other drug substances, including *e.g.*, solrimafetol hydrochloride. Ex. 1016, 391–93. For example, Kaleemullah states that its method of detecting isopropyl chloride "has been applied to various drug substances," and further discloses that it "was validated as per the ICH guideline . . . for specificity, limit of detection, limit of quantification, linearity, accuracy, precision and robustness." Ex. 1016, 399, 393. Kaleemullah also elaborates upon details of evaluating the "accuracy" and "robustness" of its disclosed method. Ex. 1016, 396–97. As such,

a POSITA would have understood that the method of detecting 2-CP as disclosed in Kaleemullah is applicable to detecting 2-CP in other drug substances, e.g., solriamfetol hydrochloride. Indeed, Kaleemullah's results of various validation parameters confirmed that the method is "specific, robust, linear, precise and accurate" and as Kaleemullah discloses, is advantageously capable of detecting 2-CP at levels as low as 0.93 ppm. Ex. 1016, Table 2. Therefore, in modifying Choi268's method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride based on the teachings in Kaleemullah of a method of detecting 2-CP in "*the composition*," a POSITA would have had a reasonable expectation of success in view of the afore-mentioned teachings of Kaleemullah. Ex. 1003, ¶66.

A POSITA would have been further motivated to combine Choi268 and Kaleemullah (i.e., modify Choi268's method of preparing solriamfetol hydrochloride to include the teachings of Kaleemullah's related to the detection of 2-CP formed in the drug substance) because to do so would have been the arrangement of old elements (a process for preparing O-carbamoyl aminoalcohols using HCl and isopropanol and gas chromatography (GC) with a flame ionization detector) with each performing the same function it has been known to perform (chemical reactions and impurity detection) and yielding no more than what one would expect from such an arrangement (an improved method of preparing a drug substance based on detecting impurities in the drug substance), as Kaleemullah

demonstrates. Indeed, Kaleemullah teaches several advantages of its method of detecting 2-CP: "The developed gas chromatographic method has to evaluate reliable and economical result for the simultaneous determination of Methyl chloride, Ethyl chloride and Isopropyl chloride residue. . . . The results of various validation parameters confirmed that the method is specific, robust, linear, precise, and accurate. The method has been applied to various drug substances containing possible alkyl chloride moiety in the drug matrix. The experimental data shows that the method has potential application for the quantitative determination of alkyl chloride moiety present in the drug substances." Ex. 1016, 399. Ex. 1003, ¶67.

In addition, a POSITA would have had a reasonable expectation of success of arriving at a solriamfetol hydrochloride composition comprising "*less than about 5 ppm*" of 2-CP because it would have required only routine experimentation to optimize the salt formation process described in Choi268 to minimize the level of genotoxic impurities (e.g., 2-CP) present in the drug substance. Indeed, Choi268 teaches that "various other embodiments and modifications in the practice of the invention," such as the synthesis described in Example 1, "will be apparent to, and can be readily made by, those skilled in the art." Ex. 1006, [0077]. It would have been within the skill of a POSITA to adjust, for example, the reagents and reaction temperatures to arrive at a lower yield of 2-CP. *See, e.g.*, Ex. 1019, 789 (disclosing that "[f]or salt formation from methanolic solutions the critical parameters were

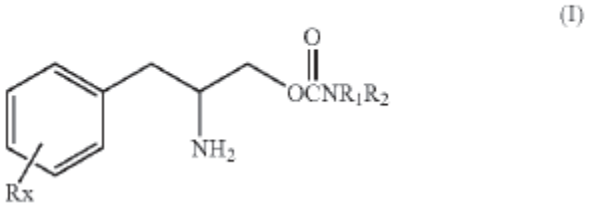
using 37% aq HCl and maintaining the slurry at 10 °C during the HCl addition," which was able to reduce genotoxic impurities down to 1ppm); *see also* Ex. 1007, 41 (disclosing that "avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a higher temperature and incorporating water into the [salt formation] process when possible would reduce the chances of formation of [] genotoxins"). Ex. 1003, ¶68.

As demonstrated above, a POSITA would be motivated to combine Choi268 and Kaleemullah, with a reasonable expectation of success. Such a person would have been further motivated to combine Choi268 and Kaleemullah based on the teachings of Ahnaou, as explained below. While Choi268 and Kaleemullah do not expressly disclose how to prepare "*[a] composition*" using "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*," it would have been obvious in view of Ahnaou. *See* Ex. 1005, [0068]. Ahnaou explains how to prepare "*[a] composition.*" Specifically, Ahnaou teaches that "[t]o prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof as the active ingredient," such as solriamfetol hydrochloride, "is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques." Ex. 1005, [0068]. As discussed above, Choi268 provides that solriamfetol hydrochloride is a "pharmaceutically useful compound[]" that is "being developed for the treatment of central nervous system (CNS) disorders, particularly

as antidepressants." Ex. 1006, [0002]. Accordingly, a POSITA would have understood that the product O-Carbamoyl-(D)-phenylalaninol hydrochloride of Choi268 can be "intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques," as taught in Ahnaou, to prepare the "*composition*." Ex. 1005, [0068]. Further, in view of Kaleemullah's teachings of an analytical method for detecting "residual" amounts of 2-CP that would form in the process for synthesizing solriamfetol hydrochloride taught in Choi268, the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting 2-CP. As such, it would have been obvious to a POSITA that the resulting "pharmaceutical composition[]" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah can be administered to patients for the treatment of neurological disorders such as narcolepsy, with a reasonable expectation of success, based on the methods disclosed in Ahnaou (*see* Ex. 1005, [0024], [0068]). Moreover, Choi268, Kaleemullah and Ahnaou commonly disclose pharmaceutical salt forms of active ingredients. Ex. 1006, [0068]–[0069]; Ex. 1016, 390–91; Ex. 1005, [0024]. Ex. 1003, ¶69.

Moreover, Ahnaou is analogous art to the 354 Patent because it similarly relates to the "fields of pharmacology, neurology and psychiatry," and provides "methods for the use of certain carbamate compounds," including solriamfetol hydrochloride, "for the treatment of sleep-wake disorders including excessive

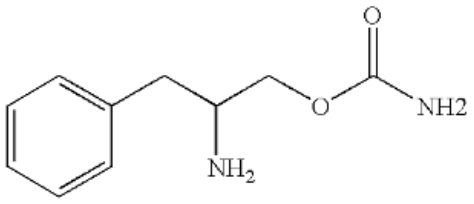
daytime sleepiness and pathological somnolence." Ex. 1005, [0002]. For these same reasons, Ahnaou is also reasonably pertinent to the purported problem addressed by the 354 Patent, i.e., "the use of . . . the APC [solriamfetol] with increased purity for the treatment of disorders responsive to APC." Ex. 1001, 1:51–54. Ahnaou discloses a "method of treating sleep disorders in a subject, including excessive daytime sleepiness (EDS) or pathological somnolence, comprising administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the Formula (I) . . . or a pharmaceutically acceptable salt or ester thereof," which includes solriamfetol hydrochloride. Ex. 1005, [0024]. Formula I in Ahnaou is reproduced below:



Ex. 1005, [0024]. Ahnaou further explains that "[e]mbodiments of the invention include a method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of Formula Ib (R)-(beta-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates."

Ex. 1005, [0028]. In other words, Ahnaou teaches O-carbomoyl-(D)-phenylalaninol (i.e., Formula Ib, which is reproduced below) as a specific embodiment of a compound of Formula I that can be used in the methods and compositions disclosed therein. As noted above, O-carbomoyl-(D)-phenylalaninol is solriamfetol hydrochloride—the same compound disclosed in Choi268 and claimed in the composition of the 354 Patent.

Formula Ib



Ex. 1005, [0028]. Ex. 1003, ¶70.

A POSITA would have been motivated to combine the teachings of Choi268 and Kaleemullah to additionally include Ahnaou because of Ahnaou's teachings related to administering "*the composition*" to a subject. For example, Ahnaou discloses "*a dosage form*." "Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. . . . The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pills can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former." Ex. 1005, [0070]. "[F]or use as a treatment for EDS, the compounds of

this invention can be employed at a daily dose in the range of about 0.1 mg to 1000 mg usually on a regimen of 1 to 3 times per day, for an average adult human." Ex. 1005, [0066]. Accordingly, a POSITA would have been motivated to modify Choi268's method of preparing solriamfetol hydrochloride to include the teachings of Kaleemullah's related to the detection of 2-CP, and additionally modified to include the teachings of Ahnaou related to administering "*the composition*." Moreover, a POSITA would have been motivated to combine the teachings of Choi268 and Kaleemullah to additionally include the teachings of the Ahnaou because of the beneficial effects of using (R)-(beta-amino-benzenepropyl) carbamate in effective reduction of sleepiness, as taught in Ahnaou. For example, Ahanou's study indicates "significant enhancement of active wakefulness . . . observed during the first 3 hours following the administration of TEST COMPOUND." Ex. 1005, [0137]; *see also* Ex. 1005, [0133]–[0138] (describing significant changes in the distribution of sleep-wake states upon administration of its TEST COMPOUND). Accordingly, in view of the therapeutic benefits of the compound demonstrated in Ahnaou's tests in treating medical disorders (e.g., excessive daytime sleepiness), a POSITA would have had a reasonable expectation of success in modifying Choi268's method of preparation of "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*," as modified by Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," to additionally include Ahnaou's

teachings related to preparing and administering "*the composition*" comprising "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" and "*2-chloropropane*." Ex. 1003, ¶71.

Therefore, for the reasons explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. Ex. 1003, ¶72.

2. Claim 1

i. *[1.0] A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and*

Choi268 and Ahnaou teach or suggest "*[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride*."

First, Choi268 discloses that "**O-carbamoyl-(D)-phenylalaninol hydrochloride** and O-carbamoyl-(L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride **are being developed for treatment of central nervous system (CNS) disorders, particularly as antidepressants**." Ex. 1006, [0002] (emphasis added). A POSITA would have understood from these

disclosures that O-carbamoyl-(D)-phenylalaninol hydrochloride, i.e., "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*," can be formulated into "[a] composition" for pharmaceutical use, including for the treatment of Central Nervous System (CNS) disorders. Ex. 1003, ¶74.

Additionally, Choi268 discloses a method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*." For example, Choi268 describes that O-Carbamoyl-(D)-phenylalaninol is first prepared, which is then used for the preparation of O-Carbamoyl-(D)-phenylalaninol hydrochloride ("*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*"). Choi268's synthesis procedure is detailed as follows:

> **Preparation of O-Carbamoyl-(D)-phenylalaninol**
>
> In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer, thermometer and 250 mL addition funnel, 838 mL of dichloromethane was charged followed by D-phenylalaninol (100 g, 0.66 mole) and sodium cyanate (85 g, 0.92 mole). The mixture was stirred in an ice-bath. The addition funnel was charged with methanesulfonic acid (222.3 g, 2.31 mol) which was slowly added to the reaction mixture so as to maintain the temperature below 5° C. The reaction mixture thickened after the completion of the addition. The ice-bath was removed and the reaction mixture was stirred until D-phenylalaninol was no longer detected by TLC analysis. To the reaction mixture, 80 grams of ice was added and the reaction mixture was cooled in an ice bath, and a 20% aqueous solution of sodium hydroxide was added at such a rate as to maintain the temperature below 5° C. until the pH of the aqueous phase was between 10 and 11 as measured by using pH paper. The mixture was transferred

> to a separatory funnel and the organic phase was separated. The aqueous phase was extracted with two 500 mL portions of dichloromethane, and the combined organic phase was washed with brine (350 mL) and dried over sodium sulfate (50 g) overnight. After removal of sodium sulfate by filtration, the organic phase was concentrated in vacuo to yield 115 g (89%) of the free base form of the desired product O-Carbamoyl-(D)-phenylalaninol as an oil.
>
> O-Carbamoyl-(D)-phenylalaninol hydrochloride was prepared as follows. The crude reaction product O-Carbamoyl-(D)- phenylalaninol (115 g) was dissolved in 120 mL of isopropanol and was transferred to three-neck round bottom flask equipped with a mechanical stirrer. **The mixture was chilled in an ice bath and the dropping funnel was charged with 100 mL of saturated HCl solution in isopropanol (6.5 M). The HCl solution was slowly added to the free base solution** so as to maintain the temperature below 5° C. During the addition, precipitation of the desired product in HCl form was observed. After the complete addition the mixture was stirred for another hour and 660 mL of acetone was added. The mixture was stirred for another hour and the white precipitate was collected by filtration. The product was washed thoroughly with ice-chilled isopropanol-acetone (⅓, v/v), and dried in vacuo. **The product O-Carbamoyl-(D)-phenylalaninol hydrochloride** weighed 110 gram (71.5%) and was a white solid.

Ex. 1006, [0068]–[0069] (emphasis added). Ex. 1003, ¶78–79. Therefore, Choi268 teaches the synthesis of "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*."

Secondly, although Choi268 does not expressly disclose how to prepare "*[a] composition*" using "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*," it would have been obvious in view of Ahnaou. For example, Ahnaou discloses

> **To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques**. Carriers are necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorings, sweeteners, preservatives, dyes, and coatings. In preparing compositions in oral dosage form, any of the usual pharmaceutical carriers may be employed. For example, for liquid oral preparations, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like.

Ex. 1005, [0068]. Therefore, Ahnaou discloses a method of preparing "*[a] composition.*" Ex. 1003, ¶75.

And further, as Dr. Lepore explains, Ahnaou's method includes the use of O-carbomoyl-(D)-phenylalaninol ("*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*")—the same compound disclosed in Choi268 and recited in the claims of the 354 Patent. Ex. 1003, ¶75–76 (citing Ex. 1005, [0028] ("Embodiments of the invention include a method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of **Formula Ib (R)-(beta-aminobenzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol)** or an enantiomeric mixture wherein the enantiomer of Formula Ib

(R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates."); *see also* Ex. 1005, [0024] (Formula Ib and Formula I).

In view of the teachings of Choi268 describing a method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" and in further view of the above-mentioned Ahnaou's teachings of a method of preparing "*[a] composition*," a POSITA would have modified Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*" resulting in "*[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride.*" *See* §VIII.A.1. Moreover, as Dr. Lepore explains, a POSITA would have understood that the product O-Carbamoyl-(D)-phenylalaninol hydrochloride of Choi268 can be "intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques," as taught in Ahnaou, to prepare the "*composition*." Ex. 1005, [0068]. Ex.1003, ¶79.

Accordingly, Choi268 and Ahnaou render obvious "*[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride*." Ex.1003, ¶80.

ii. *[1.1] 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.*

The combination of Choi268, Kaleemullah, and Ahnaou renders this element obvious.

First, Kaleemullah discloses "*2-chloropropane,*[5] *. . . less than about 5 ppm 2-chloropropane*."

Kaleemullah discloses the formation of "*2-chloropropane*." While Choi268 does not expressly disclose the formation of "*2-chloropropane*," it would have been obvious to a POSITA that "*2-chloropropane*" is formed in Choi268's synthesis of "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*," in view of Kaleemullah. Kaleemullah discloses that "**[i]sopropyl chloride may form at the salt formation step**, as ziprasidone base **in alcohol solvent** (methanol, ethanol, or **isopropanol**) **is treated with hydrochloric acid** leading to precipitate of ziprasidone hydrochloride" during the synthesis of ziprasidone hydrochloride. Ex. 1016, 391 (emphasis added); Ex. 1003, ¶¶83–84. Therefore, Kaleemullah expressly discloses the formation of "*2-chloropropane.*"

And additionally, a POSITA would have understood "*2-chloropropane*" to form during the synthesis of "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride.*" As Dr. Lepore explains, it was well-known in the prior art that "*2-chloropropane*" is produced during the salt formation process of an active ingredient, e.g., during the reaction between isopropanol and HCl, as described in Choi268's

[5] "*2-chloropropane*" or "2-CP" is also commonly referred to in the art as isopropyl chloride, as referred to in Kaleemullah.

method of preparing O-Carbamoyl-(D)-phenylalaninol hydrochloride ("*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*"). Ex. 1006, [0068]–[0069]; Ex. 1003, ¶87 (citing Ex. 1008, 168 ("**2-chloropropane was only found in the route that used hydrochloric acid** (TETS 2), and it might have been synthesized by the chlorination of 2-propanol (isopropyl alcohol) by hydrochloric acid."); Ex. 1009, Abstract ("[d]rug synthesis and/or formulation can generate **genotoxic impurities**. For instance, **strong acid/alcohol interactions** during the process of drug salt formation **produce alkylating agents such as alkyl halides** and alkyl esters of alkyl sulfonic acids.")); *see also* Ex. 1003, ¶85 (explaining the similarities between Choi268 and Kaleemullah on the basis of which a POSITA would have understood "*2-chloropropane*" to form in Choi268's method).

Furthermore, Kaleemullah's teachings—involving, for example, the use of HCl and isopropanol that results in the formation of **isopropyl chloride** ("*2-chloropropane*")—are consistent with Patent Owners' statement during prosecution that "2-CP is the product of the reaction between isopropanol and HCl." Ex.1003, ¶86 (citing Ex. 1002).

Mapping #1

Kaleemullah discloses "*less than about 5 ppm 2-chloropropane.*" Kaleemullah discloses the formation of "*2-chloropropane*" (*see* Ex. 1016, 391) as explained above, and also describes a method of detecting it at a level "*less than*

about 5 ppm" (*see* Ex. 1016, 391–93). Further, as Dr. Lepore explains, in view of Kaleemullah's teachings and a POSITA's knowledge, a POSITA would have been motivated to limit the amount of "*2-chloropropane*" present in *"[a] composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride*" to a level "*less than about 5 ppm*." Kaleemullah explains: "**[i]sopropyl chloride**" ("*2-chloropropane*") is "**reported as carcinogen,**" "**[t]herefore it is necessary that[] these residual impurities should be controlled to limits permitted by threshold of toxicological concern (TTC),**" and further that a TTC value "**estimated to be 1.5µg/person/day intake of a genotoxic impurity is considered to be associated with an acceptable risk for most pharmaceuticals as per EMEA guideline on the limit of genotoxic impurities [CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006]** as well as risk assessment literature." Ex. 1016, 391 (emphasis added); Ex. 1003, ¶¶88–89.

Moreover, Dr. Lepore explains the reasons as to why genotoxic impurities in drug substances should be limited to a value of 1.5µg/day. Ex. 1003, ¶90 (citing Ex. 1018, 6 ("for application of a TTC in the assessment of **acceptable limits of genotoxic impurities in drug substances [at] a value of 1.5 µg/day corresponding to a 10^{-5} lifetime risk of cancer can be justified as for pharmaceuticals a benefit exists**.")). Dr. Lepore further explains as to why 1.5µg/day is the upper limit in terms of the level of genotoxic impurities (e.g., "*2-chloropropane*") present in a drug

composition and therefore a POSITA would have recognized that it is desirable to control the limit of genotoxic impurities to less than 1.5μg/day. Ex.1003, ¶90 (citing Ex. 1018, 6 ("A TTC value higher than 1.5 μg/day may be acceptable under certain conditions, e.g. short-term exposure, for treatment of a life-threatening condition, when life expectancy is less than 5 years, or where the impurity is a known substance and human exposure will be much greater from other sources (e.g. food).")).

Additionally, a POSITA would have understood that a limit of 1.5μg/person/day translates to "*less than about 5 ppm*." For example, the EMEA guidelines (cited in Kaleemullah) disclose a mathematical formula for translating TTC (expressed in μg/day) to a concentration limit (expressed in ppm). Specifically, the EMEA guidelines explain that:

> The concentration limits in ppm of genotoxic impurity in drug substance derived from the TTC can be calculated based on the expected daily dose to the patient using equation (1).
>
> (1) Concentration limit (ppm)= $\frac{\text{TTC [μg/day]}}{\text{dose (g/day]}}$

Ex. 1018, 6. Therefore, a POSITA reading Kaleemullah would have understood to use this formula for translating a TTC value disclosed in Kaleemullah to a corresponding ppm value. Ex. 1003, ¶91.

Moreover, a POSITA would have known to assume a daily dose of 1000 mg API (or, equivalently 1.0g of API) in the above-mentioned formula. As Dr. Lepore

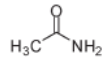
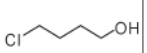
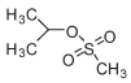
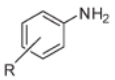
explains, at the time of the claimed invention, it would have been within a POSITA's knowledge to assume a daily dose of 1.0g of API for conservatively determining genotoxic impurity (GTI) limits. Ex. 1003, ¶92 (citing Ex. 1017, Table 2, footnote d. (disclosing the use of "**a daily dose of 1000 mg API**") and 987 ("In all cases, an acceptable toxicology limit based on a two-year dosing duration, **an API dose of 1000 mg**, and the risk assessment methodology described below are substantially higher than limits determined using current risk assessment parameters.") Accordingly, using the above-mentioned formula of the EMEA guidelines, Kaleemullah's description of the formation of "isopropyl chloride" ("*2-chloropropane*") as a carcinogen/genotoxic impurity that is limited to an estimated TTC value of "1.5µg/person/day intake" and a POSITA's knowledge of assuming a daily dose of 1.0g of API, a POSITA would have understood that Kaleemullah discloses the formation of "*2-chloropropane*" and limiting its intake to "*less than about 5 ppm*." Ex. 1003, ¶92. Therefore, Kaleemullah discloses "*2-chloropropane …less than about 5 ppm 2-chloropropane*." Ex. 1003, ¶92.

Courts have held that a prior-art reference that discloses a value within a claimed range invalidates the claimed range. *See Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 31 (Fed. Cir. 2020) ("[T]his court [has] recognized that '[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.'") (quoting *In re*

Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003)); *see also Ex Parte Marek Z. Kubin and Raymond G. Goodwin*, 83 U.S.P.Q.2d 1410, 2007 WL 2070495, *4 (Bd. Pat. App. & Interf. 2007) ("A single, obvious species within a claimed genus renders the claimed genus unpatentable under § 103.); *cf. Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 934-35 (Fed. Cir. 2003) ("[I]t is an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated if one of them is in the prior art") (quotation omitted).

Furthermore, at the time of the claimed invention, a POSITA would have understood the need to limit the level of "*2-chloropropane*" to "*less than about 5 ppm*." For example, Callis reflecting the knowledge of a POSITA, provides toxicology limits for "*2-chloropropane.*" Specifically, Table 2 in Callis shows that the "acceptable lifetime cumulative dose (daily chronic limit)" of "isopropyl chloride" ("*2-chloropropane*") is "1.5ppm." Ex. 1017, Table 2.

Table 2. **Toxicology limits for genotoxic impurities (GTIs)**

Compound	GTI Category[a]	Carcinogenicity Slope Factor (CSF)[b]	Acceptable Lifetime Cumulative Dose[c] *(daily chronic limit)*[d]	Acceptable 2-year weekly dose *(short-term limit)*[d]	Chosen limit for 2-year weekly dosing[e]
Acetamide 	Category 1 (Animal carcinogen)[f]	0.07/mg/kg/day[g]	255 mg *(10 ppm)*	2450 mcg[h] *(2450 ppm)*	1000 ppm[i]
Hydrazine H_2N-NH_2	Category 1 (Animal Carcinogen)[j]	3.0/mg/kg/day[j]	5960 mcg *(0.2 ppm)*	50 mcg[k] *(50 ppm)*	50 ppm
Isopropyl Chloride 	Category 2 (+ Ames)	NA[l]	TTC at 38 mg *(1.5 ppm)*	350 mcg[m] *(350 ppm)*	350 ppm
4-Chloro-1-butanol 	Category 2 (+ Ames)	NA[l]	TTC at 38 mg *(1.5 ppm)*	350 mcg[m] *(350 ppm)*	350 ppm
Isopropyl mesylate 	Category 2 (+ Ames)[n]	NA[l]	TTC at 38 mg *(1.5 ppm)*	350 mcg[m] *(350 ppm)*	350 ppm
Aniline Alert 	Category 3 (Structural Alert)	NA[l]	TTC at 38 mg *(1.5 ppm)*	350 mcg[m] *(350 ppm)*	350 ppm

Ex. 1017, Table 2 (annotated). Ex. 1003, ¶93.

Moreover, a POSITA would have had a reasonable expectation of success of arriving at a solriamfetol hydrochloride composition comprising "*less than about 5 ppm*" of "*2-choloropropane*." This is because, and as Dr. Lepore explains, it would have required only routine experimentation to optimize the salt formation process described in Choi268 to minimize the level of genotoxic impurities (e.g., "*2-choloropropane*") present in the drug substance. Ex. 1003, ¶94 (citing Ex. 1006,

[0077] (disclosing that "It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those skilled in the art"); Ex. 1019, 789 (disclosing that "[f]or salt formation from methanolic solutions the critical parameters were using 37% aq HCl and maintaining the slurry at 10 °C during the HCl addition," which was able to reduce genotoxic impurities down to 1ppm); Ex. 1007, 41 (disclosing that "avoiding strongly acidic conditions and prolonged exposure of acids to an alcohol at a higher temperature and incorporating water into the [salt formation] process when possible would reduce the chances of formation of [] genotoxins").

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Kaleemullah's teachings limiting intake of genotoxic impurities to an estimated TTC value of "1.5µg/person/day," such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of

Choi268/Ahnaou/Kaleemullah "*comprises less than about 5 ppm 2-choloropropane*." Ex. 1003, ¶95. Therefore, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious "*2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane.*"

Mapping #2[6]

Furthermore, for the additional reasons set forth below, Kaleemullah discloses "*2-chloropropane . . . less than about 5 ppm 2-chloropropane.*" Ex.1003, ¶96.

First, as of the priority date, a POSITA would have understood the increased concern to limit genotoxic impurities (such as 2-CP) in drug substances to levels that are as low as possible. Ex. 1014, Abstract ("Genotoxic impurities (GTIs) in pharmaceuticals at trace levels are of increasing concerns to both pharmaceutical industries and regulatory agencies due to their potentials for human carcinogenesis. Determination of these impurities at ppm levels requires highly sensitive analytical methodologies . . . in pharmaceutical R&D."); Ex. 1015, 993 (recognizing the need for "developing and validating methods to measure trace levels of genotoxic impurities."); Ex. 1007, 422 ("Even small amounts of residual alcohol in API can,

[6] As explained below, the analysis for Mapping #2 satisfies the requirements of claim 2 which requires "*wherein the composition comprises less than about 1 ppm 2-chloropropane*."

in principle, interact with a strong acid used in the downstream formulation process to produce trace amounts of a genotoxin in the drug product."). Indeed, the need to reduce genotoxin levels in drugs to limits even lower than toxicology-based requirements (e.g., lower than 1.5µg/person/day) was well within the knowledge of POSITA. For example, the EMEA guidelines (cited in Kaleemullah) state that "**pharmaceutical measurements should be guided by a policy of controlling levels to "as low as reasonably practicable" (ALARP principle), where avoiding is not possible**." Ex. 1018, 5 (emphasis added).

> **5.2 Genotoxic Compounds Without Sufficient Evidence for a Threshold-Related Mechanism**
>
> The assessment of acceptability of genotoxic impurities for which no threshold mechanisms are identified should include both pharmaceutical and toxicological evaluations. In general, pharmaceutical measurements should be guided by a policy of controlling levels to "as low as reasonably practicable" (ALARP principle), where avoiding is not possible. Levels considered being consistent with the ALARP principle following pharmaceutical assessment should be assessed for acceptability from a toxicological point of view (see decision tree & following sections).

Ex. 1018, 5. Therefore, in view of the teachings of the ALARP principle, a POSITA would have understood to lower the level of genotoxic impurities such as "*2-chloropropane*" in drug substances to "*less than about 5 ppm*." Ex. 1003, ¶97. Furthermore, Callis reflecting the knowledge of a POSITA, emphasizes the importance of the ALARP principle to achieve limits even lower than toxicology-based requirements. Callis states "[c]onsideration of the ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require" and further that "GTI control typically must be

demonstrated at very low (ppm) levels in the API or synthetic intermediates." Ex. 1017, 986. As such, Callis teaches that, "[w]hen considering potential risk to the patient, genotoxic impurities must often be controlled to much lower levels than required by the ICH Q3A(R2) guideline for non-GTIs." Ex. 1017, 990. Consequently, at least in view of the supported teachings of these references, a POSITA would have understood the increased concern to limit genotoxic impurities in drug substances. Ex.1003, ¶97.

In addition, Kaleemullah discloses "*2-chloropropane . . . less than about 5 ppm 2-chloropropane.*" As explained above, Kaleemullah discloses the formation of "*2-chloropropane*" (*see* Ex. 1016, 391) and Kaleemullah describes a method of detecting "isopropyl chloride" ("*2-chloropropane*") (*see* Ex. 1016, 391–93). Further, Kaleemullah's Table 2 shows the lowest concentration of isopropyl chloride ("*2-chloropropane*") that can be detected in a sample of a drug substance (i.e., the limit of detection).

Table 2. Evaluation of LOD and LOQ, Linearity data

Components	Methyl Chloride	Ethyl Chloride	Isopropyl Chloride
Concentration (µg/g)	8.8	8.8	9.1
S/N ratio	35.0	36.8	32.2
Limit of detection (µg/g)	0.83	0.79	0.93
Limit of quantification (µg/g)	2.51	2.39	2.83
Limit of detection precision (%RSD)[a]	12.9	13.4	10.9
Limit of quantification precision(%RSD) [a]	2.4	3.2	2.7
Slope	1105.1	1623.5	5112.7
STEY X	146.0	116.1	886.4
Correlation Co-efficient	0.9996	0.9999	0.9993
RSQ(r^2)	0.9992	0.9998	0.9986

[a] *Average of n=6 determinations*

Ex. 1016, Table 2 (annotated). Specifically, Table 2 indicates that "[l]imit of detection (µg/g)" is "0.93" and that "[l]imit of detection precision (%RSD)" is "10.9" for isopropyl chloride. This means that Kaleemullah teaches that the limit of detection (LOD) for 2-CP in its analytical method is 0.93 µg/g ± 10.9%. Because, mathematically, the unit of µg/g is equivalent[7] to parts per million (ppm), Kaleemullah demonstrates that its analytical method detects "*2-chloropropane*" at concentrations as low as 0.93 ppm ± 0.10 ppm. In other words, the limit for detecting "*2-chloropropane*" ranges from an upper limit of 1.03 ppm (= 0.93 + 0.10) to a lower

[7] *See* Microgram/gram (ug/g) Unit Conversions, CONVERTN, https://convertn.com/concentration_percentage/microgram_gram.html (last visited Sept. 18, 2024).

limit of 0.83 ppm (= 0.93 - 0.10). Indeed, Kaleemullah confirms that its method of detecting isopropyl chloride "has been applied to various drug substances," and further discloses that it "was validated as per the ICH guideline . . . for specificity, limit of detection, limit of quantification, linearity, accuracy, precision and robustness." Ex. 1016, 399, 393. Further, Kaleemullah's "experimental data shows that the method has potential application for the quantitative determination of alkyl chloride moiety present in the drug substances." Ex. 1018, 399; Ex.1003, ¶98. Therefore, Kaleemullah discloses "*2-chloropropane . . . less than about 5 ppm 2-chloropropane*" for this additional reason. Ex.1003, ¶98.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Kaleemullah's Table 2 indicating that the limit of detection is 0.93μg/g (equivalently, 0.93ppm), such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah

"*comprises less than about 5 ppm 2-chloropropane*." Ex.1003, ¶99. Therefore, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious "*2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane*" for this additional reason.

Therefore, for the reasons above, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious claim 1. Ex. 1003, ¶100.

3. Claim 2

i. *[2.0] The composition of claim 1, wherein the composition comprises less than about 1 ppm 2-chloropropane.*

For the same reasons discussed above, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious this claim element. *See* explanation with respect to Mapping #2 in element [1.1] above. As explained earlier, Kaleemullah citing the EMEA guidelines, discloses an estimated TTC value of "1.5µg/person/day" for the "intake of a genotoxic impurity," (e.g., "*2-choloroproane*"), which translates to 1.5ppm (assuming[8] a daily dose of 1.0g of the API). However, as Dr. Lepore explains, a POSITA would be motivated to control genotoxic impurities to further reduce it to levels that are lower than 1.5 ppm,

[8] A POSITA would have understood to assume a daily dose of 1.0g of API for determining genotoxic impurity (GTI) limits. *See* Ex. 1017, Table 2, footnote d.

including "*less than about 1 ppm*." Ex. 1003, ¶101 (citing Ex. 1018, 5 (disclosing "as low as reasonably practicable" (ALARP principle)); *see also* Ex. 1017, 986 ("**Consideration of the ALARP principle (as low as reasonably practicable) for impurities may achieve tighter control than toxicology-based limits require**." . . . "**GTI control typically must be demonstrated at very low (ppm) levels in the API** or synthetic intermediates."), 990 ("When considering potential risk to the patient, genotoxic impurities must often be controlled to much lower levels than required by the ICH Q3A(R2) guideline for non-GTIs."). Kaleemullah expressly discloses that its "[l]imit of detection (µg/g)" for isopropyl chloride ("*2-chloropropane*") is "0.93" ppm. Ex. 1016, 393 and Table 2. Indeed, Kaleemullah confirms that its method of detecting isopropyl chloride "has been applied to various drug substances," and further discloses that it "was validated as per the ICH guideline . . . for specificity, limit of detection, limit of quantification, linearity, accuracy, precision and robustness." Ex. 1016, 399, 393.

Table 2. Evaluation of LOD and LOQ, Linearity data

Components	Methyl Chloride	Ethyl Chloride	Isopropyl Chloride
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Limit of quantification precision(%RSD)[a]	2.4	3.2	2.7
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STEY X	146.0	116.1	886.4
Correlation Co-efficient	0.9996	0.9999	0.9993
RSQ(r^2)	0.9992	0.9998	0.9986

[a] *Average of n=6 determinations*

Ex. 1016, Table 2 (annotated). Therefore, Kaleemullah discloses "*less than about 1 ppm 2-chloropropane*." Ex. 1003, ¶102.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Kaleemullah's Table 2 indicating that the limit of detection of "*2-chloropropane*" is 0.93µg/g (equivalently, 0.93ppm), it would have been obvious to a POSITA that "*the composition*" prepared according to the combined teachings of

Choi268/Ahnaou/Kaleemullah "*comprises less than about 1 ppm 2-chloropropane*." Ex. 1003, ¶103.

Therefore, the combination of Choi268, Kaleemullah, and Ahnaou renders obvious "*[t]he composition of claim 1, wherein the composition comprises less than about 1 ppm 2-chloropropane.*" Ex. 1003, ¶103.

4. Claim 3

i. *[3.0] The composition of claim 1, wherein the composition is a dosage form.*

The combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 3. Ex. 1003, ¶104.

In addition, Ahnaou discloses "*a dosage form*." For example, Ahnaou teaches that "**[p]referably these compositions are in unit dosage forms** such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories, for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation." Ex. 1005, [0072]. In addition, "[t]he compound may be administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral." Ex. 1005, [0067]. "Because of their ease in administration, **tablets and capsules represent the most advantageous oral dosage unit form**, in which case solid pharmaceutical carriers are obviously

employed. . . . The tablets or pills can be coated or otherwise compounded to **provide a dosage form** affording the advantage of prolonged action. For example, the tablet or pills can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former." Ex. 1005, [0070] (emphasis added). Therefore, Ahnaou discloses "*a dosage form*." Ex. 1003, ¶¶105, 109.

As explained above, it would have been obvious to a POSITA that Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" would be modified based on Ahnaou's teachings of a method of preparing "*[a] composition*," and in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane.*" *See* §VIII.A.1. And, in further view of Ahnaou's disclosure of "*a dosage form*," such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is a dosage form*." Ex. 1003, ¶106.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious "*[t]he composition of claim 1, wherein the composition is a dosage form*." Ex. 1003, ¶107.

5. Claim 4

i. *[4.0] The composition of claim 3, wherein the composition is an immediate release oral dosage form.*

For the same reasons discussed above, the combination of Choi268, Kaleemullah and Ahnaou renders obvious this claim element. *See* [3.0] above related to "*the composition is . . . [a] dosage form*." Ex. 1003, ¶108.

Furthermore, Ahnaou discloses "*immediate release oral dosage form*." For example, Ahnaou explains that "compounds of Formula (I) can be . . . [in] forms suitable for oral administration [that] include solid forms, such as **pills, gelcaps, tablets, caplets, capsules (each including immediate release**, timed release and sustained release **formulations**), granules, and powders. Forms suitable for oral administration also include liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. In addition, forms useful for parenteral administration include sterile solutions, emulsions and suspensions." Ex. 1005, [0067] (emphasis added). Therefore, Ahnaou discloses "*an immediate release oral dosage form*." Ex. 1003, ¶109.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be

additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Ahnaou's disclosure of "*an immediate release oral dosage form*," such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is an immediate release dosage form*." Ex. 1003, ¶110.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious "*[t]he composition of claim 3, wherein the composition is an immediate release oral dosage form*." Ex. 1003, ¶111.

6. Claim 5

i. *[5.0] The composition of claim 4, wherein the composition is a tablet or a capsule.*

The combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 5. Ex. 1003, ¶112.

In addition, Ahnaou discloses "*a tablet or a capsule.*" *See* [3.0] and [4.0] above. Ex. 1003, ¶113.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation

and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Ahnaou's disclosure of "*a tablet or a capsule*," such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is a tablet or a capsule*." Ex. 1003, ¶114.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious "*[t]he composition of claim 4, wherein the composition is a tablet or a capsule*." Ex. 1003, ¶115.

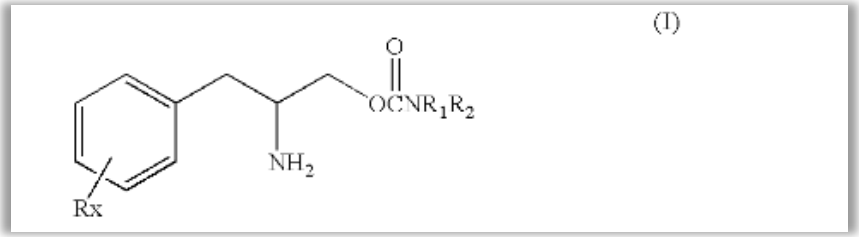
7. Claim 6

i. *[6.0] A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the composition of claim 1.*

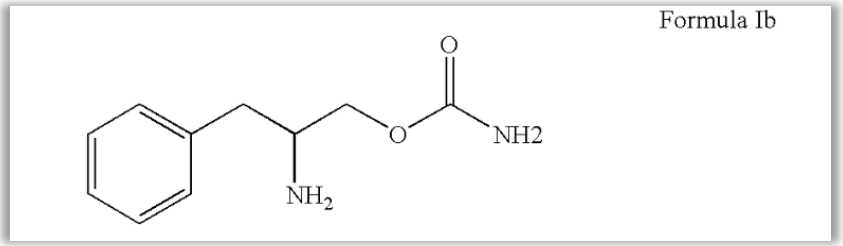
The combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 6. Ex. 1003, ¶116.

In addition, Ahnaou discloses "*[a] method of treating narcolepsy, . . . excessive daytime sleepiness . . . attention deficit/hyperactivity disorder, . . . depression, bipolar disorder . . . in a subject in need thereof.*" For example, Ahnaou

discloses that "[t]he present invention is directed to **a method of treating sleep disorders in a subject, including excessive daytime sleepiness (EDS) or pathological somnolence comprising, administering to a subject in need of such treatment, a therapeutically effective amount of a compound of the Formula (I)**" including solriamfetol hydrochloride. Ex. 1005, [0024]; *see also* [0030] (disclosing "[e]mbodiments of the invention include a methods wherein the cause of the **EDS** is chosen from the group consisting of . . . **narcolspesy . . . Attention Deficit Hyperactivity Disorder (ADHD), . . . Major Depression, Bipolar Disorde**r"). "Embodiments of the invention include the use, for the preparation of **a medicament for the treatment of EDS, of an enantiomer selected from the group consisting of Formula I.**" Ex. 1005, [0027] (emphasis added).



Ex. 1005, [0027]. "Embodiments of the invention include a method include the use of an enantiomer of Formula I substantially free of other enantiomers that is the enantiomer of **Formula I b (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol)** or an enantiomeric mixture wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates." Ex. 1005, [0028] (emphasis added).



Ex. 1005, [0028]. "**Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol)** wherein the enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 90% or greater. More preferably, an enantiomer of Formula Ib (R)-(beta-amino-benzenepropyl) carbamate or (O-carbamoyl-(D)-phenylalaninol) predominates to the extent of about 98% or greater." Ex. 1005, [0029]; Ex. 1003, ¶117. Therefore, Ahnaou discloses "*[a] method of treating narcolepsy, . . . excessive daytime sleepiness . . . attention deficit/hyperactivity disorder, . . . depression, bipolar disorder . . . in a subject in need thereof.*" Ex. 1003, ¶117.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined

teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And moreover, in further view of Ahnaou's afore-mentioned disclosures, such a person would have found it obvious that "*the composition of claim 1*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou can be "*administer[ed] to [a] subject*" in "*[a] method of treating narcolepsy, . . . excessive daytime sleepiness . . . attention deficit/hyperactivity disorder, . . . depression, bipolar disorder . . . in [the] subject.*" Ex. 1003, ¶118.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 6. Ex. 1003, ¶119.

8. Claim 7

i. *[7.0] The method of claim 6, wherein the composition is administered once per day.*

The combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 7. Ex. 1003, ¶120.

Ahnaou discloses "*administer[ing] once per day*." Ahnaou discloses "for use as a treatment for EDS, **the compounds of this invention can be employed at a daily dose** in the range of about 0.1 mg to 1000 mg **usually on a regimen of 1** to 3 **time[] per day**, for an average adult human." Ex. 1005, [0066] (emphasis added); *see also* Ex. 1005, claim 14 (disclosing administration of (R)-2-amino-3-phenylpropyl carbamate and pharmaceutically acceptable salts thereof for the

treatment of, e.g., excessive daytime sleepiness). Therefore, Ahnaou discloses "*administer[ing] once per day*." Ex. 1003, ¶121.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Ahnaou's afore-mentioned disclosures, such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is administered once per day*." Ex. 1003, ¶122.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 7. Ex. 1003, ¶123.

9. Claim 8

i. *[8.0] The method of claim 6, wherein the composition is administered more than once per day.*

For the same reasons discussed above, the combination of Choi268, Kaleemullah and Ahnaou renders obvious claim 8. *See* [7.0] above.

In addition, Ahnaou discloses "*administer[ing] more than once per day*." Ahnaou discloses "for use as a treatment for EDS, **the compounds of this invention can be employed at a daily dose** in the range of about 0.1 mg to 1000 mg **usually on a regimen of 1 to 3 times per day**, for an average adult human." Ex. 1005, [0066] (emphasis added). Therefore, Ahnaou discloses "*administer[ing] more than once per day*." Ex. 1003, ¶125.

As explained above, a POSITA would have been motivated to modify Choi268's method of preparing "*(R)-2-amino-3-phenylpropyl carbamate hydrochloride*" based on Ahnaou's teachings of a method of preparing "*[a] composition*." And, moreover, in view of Kaleemullah's teachings of the formation and detection of "*2-chloropropane*," the Choi268/Ahnaou combination would be additionally modified to include Kaleemullah's method of detecting "*2-chloropropane*" resulting in "*a composition*" prepared according to the combined teachings of Choi268/Ahnaou/Kaleemullah. *See* §VIII.A.1. And, in further view of Ahnaou's afore-mentioned disclosures, such a person would have found it obvious that "*the composition*" prepared according to the combined teachings of Choi268/Kaleemullah/Ahnaou "*is administered more than once per day*." Ex. 1003, ¶126.

Therefore, the combination of Choi268, Kaleemullah and Ahnaou renders obvious "*[t]he method of claim 6, wherein the composition is administered more than once per day*." Ex. 1003, ¶127.

IX. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION AND DENY INSTITUTION

A. The Board Should Not Deny Institution Under 35 U.S.C. § 325(d)

The Board should not exercise its discretion under §325(d) to deny institution. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017- 01586, Paper 8, 17–18 (Dec. 15, 2017) (precedential); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469 Paper 6 at 9–11 (Feb. 13, 2020) (precedential). With respect to first part of the *Advanced Bionics* framework—including *Becton, Dickinson* factors (a), (b), and (d)—one of the references presented in this petition was previously before the Examiner: Choi268. However, Choi268 was only cited in an IDS and never applied by the Examiner. *See GMG Prods. LLC v. Traeger Pellet Grills LLC*, PGR2019-00024, Paper 17, at 27 (July 17, 2019) (listing on an IDS alone "does not favor denying institution" because "the Examiner did not provide any detailed assessment of [the prior art, and], instead, only indicat[ed] the references had been considered"). The remaining references—Kaleemullah and Ahnaou—were never before the Office with respect to the 354 Patent, and certainly not in combination with Choi268. That the prior art relied on, much less the combinations presented in this Petition, were not expressly addressed

by the examiner, weighs strongly in favor of institution. *See, e.g.*, *Lifecore Fitness v. Woodway USA*, IPR2024-00083, Paper 13 at 22 (May 17, 2024) (refusing to deny institution under step one of *Advanced Bionics* even though some of the references were cited on the face of the patent because of Petitioner's reliance on new art that was not previously presented to the PTO); *JUUL Labs. v. NJOY*, IPR2024-00160, Paper 9 at 5 (May 24, 2024) (*Advanced Bionics* part one not met because "mere prior citation of prior art in an IDS will not automatically satisfy the first prong"). Accordingly, in view of the entirety of the Ground advanced in this Petition, "the same or substantially the same prior art or arguments" were not previously presented to or considered by the Office so there is no need to analyze *Advanced Bionics* part two.

Nevertheless, to the extent the Board considers part two of the *Advanced Bionics* framework, it also supports not exercising discretion to deny under §325(d). For example, material error by the Office "may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Advanced Bionics*, Paper 6, at 3 n.9. The Examiner erred here in a way that was material to patentability because they did not appreciate Choi268's disclosure and also did not have the benefit of analyzing Choi268's disclosure in view of Kaleemullah and Ahnaou. In addition, the Examiner also did not have the benefit of Dr. Lepore's detailed expert testimony and the further

evidence of record. For at least these reasons, the Board should not discretionarily deny institution under §325(d).

B. The Board Should Not Deny Institution Under 35 U.S.C. § 314(a)

1. No Evidence Regarding a Stay

Factor 1, for example, is **neutral** because no request for stay has been filed. *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15 at 12 (May 13, 2020) (informative) (explaining that factor 1 generally "does not weigh for or against discretionary denial" when neither party has requested a stay); *Amazon Web Services et al. v. Zentian Ltd.*, IPR2023-01194, Paper 10 at 11 (Jan. 10, 2024) ("As to factor 1, there is no evidence as to whether there will be a stay in the parallel case, so we regard this factor as neutral.").

2. Parallel Proceeding Trial Date

No trial date has been set. Ex. 1013, 7. According to the most recent statistics[9] on median time-to-trial for civil actions in the District Court of New Jersey, the median time from filing to trial was 57.8 months. The related litigation was filed in September 2023, so trial can be expected in approximately July 2028. Any Final

[9] Comparison of Districts Within the First Circuit, U.S. Courts, https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distcomparison0630.2024.pdf (last visited Sept. 23, 2024).

Written Decision can be expected in March 2026, more than two years before trial. Accordingly, this factor **weighs against** discretionary denial.

3. Parallel Proceeding Investment

Factor 3 **weighs against** discretionary denial. In the related litigation, the parties are scheduled to exchange proposed terms for Claim Construction in November 2024 according to the amended schedule, and the investment by the parties has been relatively minimal. In addition, claim 8 is not at issue in the related litigation. *Samsung Bioepis Co. Ltd v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00739, Paper 9 at 57 (Oct. 20, 2023) ("[B]ecause certain of the challenged claims, . . . are not expressly at issue in the district court litigation, *Fintiv* factor 3 favors institution.").

4. Overlapping Issues with the Parallel Proceeding

Regarding factor 4, in the district court litigation, only a subset of the claims that are being challenged in this Petition are asserted. Thus, this factor also **weighs against** discretionary denial. *See Fintiv* Factor 3 analysis.

5. Overlapping Parties

Factor 5 is **neutral**. The Petitioner is a defendant in the related litigation. As *Fintiv* demonstrates, this factor should play a role only where a Petitioner is unrelated to a defendant in a district court proceeding. *Fintiv*, IPR2020-00019, Paper 11 at 13–14. *Fintiv* "says nothing about situations in which the petitioner is

the same as, or is related to, the district court defendant." *Id.* Accordingly, the Board should find this factor to be **neutral**.

6. Strength of Petition and Other Considerations

Other circumstances **weigh against** discretionary denial. Here, the merits of the Petition are particularly compelling—for example, Choi268 is analogous to that of the 354 Patent because it is in the field of pharmaceutical chemistry, and is directed at the same problem as the 354 Patent of synthesizing O-Carbamoyl-(D)-phenylalaninol free base (i.e., solriamfetol). The evidence presented, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence.

X. CONCLUSION

Claims 1-8 of the 354 Patent are unpatentable for the reasons demonstrated above.

Dated: September 24, 2024

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains less than 14,000 words (as determined by the Microsoft Word word-processing system used to prepare the brief and including annotations to the figures), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 24th day of September, 2024, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by priority mail on the following:

Dated: September 24, 2024

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CLAIM LISTING

Claim 1
[1.0] A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and
[1.1] 2-chloropropane, wherein the composition comprises less than about 5 ppm 2-chloropropane
Claim 2
[2.0] The composition of claim 1, wherein the composition comprises less than about 1 ppm 2-chloropropane.
Claim 3
[3.0] The composition of claim 1, wherein the composition is a dosage form.
Claim 4
[4.0] The composition of claim 3, wherein the composition is an immediate release oral dosage form.
Claim 5
[5.0] The composition of claim 4, wherein the composition is a tablet or a capsule.
Claim 6
[6.0] A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the composition of claim 1.
Claim 7
[7.0] The method of claim 6, wherein the composition is administered once per day.
Claim 8
[8.0] The method of claim 6, wherein the composition is administered more than once per day.