

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

**PATENT OWNER PRELIMINARY RESPONSE
PURSUANT TO 35 U.S.C. § 313 AND 37 C.F.R. § 42.107**

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LIST OF EXHIBITS

EX	Description
2001	Declaration of Dr. Leonard J. Chyall
2002	Sunosi Label 2023
2003	Sunosi Approval Letter
2004	Sunosi Treatment Guide
2005	Geodon Label 2022
2006	Risperdal Label 2022
2007	Uroxatrol Label 2020
2008	Valcyte Label 2021
2009	Prozac Label 2023
2010	U.S. Patent No. 5,955,499
2011	U.S. Patent No. 4,831,031
2012	Complaint, Docket No. 1, September 13, 2023
2013	Notice of Filing Date Accorded to Petition and Time for Filing Patent Owner Preliminary Response
2014	Excerpt from Defendants' Joint Invalidity Contentions, June 18, 2024
2015	Excerpts from Yuri Kazakevich & Rosario LoBrutto, HPLC for Pharmaceutical Scientists (2007)
2016	<i>Curriculum Vitae</i> of Dr. Leonard J. Chyall
2017	U.S. Patent No. 5,312,925
2018	U.S. Patent No. 8,178,674
2019	U.S. Patent Application Publication No. 2005/01433961
2020	Canadian Patent Application No. 2,549,244
2021	European Patent Application No. 0,380,924

I. INTRODUCTION

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107(a), Patent Owners SK Biopharmaceuticals Co., Ltd., and Axsome Malta Ltd.¹ submit this Preliminary Response to Petitioner Hikma Pharmaceuticals USA Inc.’s (“Petitioner”) Petition (“Pet.”) seeking *inter partes* review of claims 1–8 of U.S. Patent No. 11,560,354 (“the ’354 patent”). Institution should be denied.

Each claim of the ’354 patent is directed to compositions comprising: (1) the active pharmaceutical ingredient (“API”) (R)-2-amino-3-phenylpropyl carbamate hydrochloride (“solriamfetol hydrochloride”); and (2) minimal, non-zero amounts of 2-chloropropane (a/k/a isopropyl chloride)—less than about 5 parts per million (“ppm”) or less than about 1 ppm.

The ’354 patent specification details how the patentee repeatedly tried, but *failed*, to successfully synthesize compositions of solriamfetol hydrochloride with minimal amounts of 2-chloropropane. Ex. 1001 at 10:53-11:27. Despite these repeated, real-world failures leading up to the inventions of the ’354 patent, Petitioner argues that the claimed inventions would have been obvious. As

¹ Axsome holds all substantial rights in the ’354 patent. Therefore, throughout this Preliminary Response, Patent Owners are referred to as “Axsome.”

explained below, Petitioner's argument suffers from several fatal flaws, each of which provides an independent basis to deny institution.

First, Petitioner fails to demonstrate that there was a problem in the prior art with 2-chloropropane being present as an impurity in solriamfetol hydrochloride that would have motivated a person of ordinary skill in the art ("POSA") to attempt to minimize the impurity. In fact, the asserted art fails to disclose, teach, or suggest solriamfetol hydrochloride with *any* 2-chloropropane. Instead, Petitioner argues the prior art discloses that, when an API with an amine base moiety (like solriamfetol) is converted to its hydrochloride salt using hydrochloric acid ("HCl") and isopropyl alcohol ("IPA"), 2-chloropropane will necessarily result. The references that Petitioner relies on, however, directly contradict this argument. Thus, there is nothing in the prior art that would have taught a POSA that 2-chloropropane was an impurity that posed a potential problem for solriamfetol hydrochloride. Consequently, Petitioner fails to demonstrate that a POSA would have been motivated to even attempt to arrive at the claimed minimal-impurity compositions in the first place. Under Federal Circuit law, if the problem was unknown, the inventive solution cannot be obvious.

Second, even if one were to accept Petitioner's argument that 2-chloropropane will necessarily result from the synthesis of solriamfetol with HCl and IPA, Petitioner fails to explain why a POSA would have been motivated to continue to

use IPA in the synthesis of solriamfetol hydrochloride. Petitioner points to prior art to argue that 2-chloropropane is genotoxic. The prior art discloses that while HCl is necessary for the synthesis of hydrochloride salts of actives, IPA is not. Instead, other solvents can be used, including for the synthesis of solriamfetol hydrochloride. Petitioner does not address any of these other solvents. Federal Circuit law is clear: if there are safety concerns with using an ingredient in the prior art, then there is no motivation to select that ingredient for further use. Petitioner fails to show otherwise.

Third, Petitioner fails to demonstrate a reasonable expectation of success in arriving at the claimed minimal-impurity solriamfetol hydrochloride compositions. Both the Petition and the expert declaration allege a reasonable expectation of success attributed to “routine experimentation.” Both, however, simply quote two references that have *nothing* to do with solriamfetol hydrochloride and both fail to explain why a POSA would have *any* expectation, let alone a reasonable one, that the reaction conditions quoted would successfully result in the claimed compositions. This attorney argument and conclusory expert testimony are entitled to no weight. They are also contradicted by the real-world failures documented in the ’354 patent, which further evidence nonobviousness under Federal Circuit law.

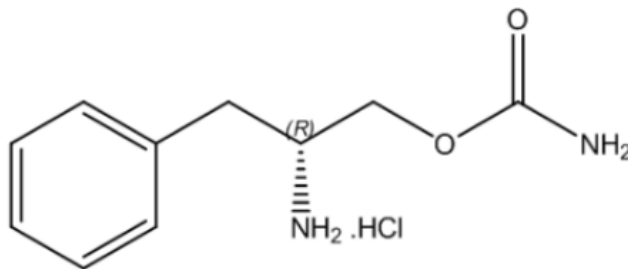
In addition to its merit-based failures, Petitioner fails to sufficiently explain why institution should not be denied under 35 U.S.C. § 314(a). Petitioner is one of four generic-pharmaceutical-company defendants already making the same

invalidity arguments made here in a parallel litigation in the District of New Jersey (the “DNJ Litigation”). Petitioner waited to file its Petition until the last possible minute, and the DNJ Litigation will likely have a decision on the ’354 patent around the same time that a Final Written Decision would issue here. Worse yet, there would be no estoppel because the other three defendants in the DNJ Litigation are not real parties in interest here. All *Fintiv* factors weigh in favor of denying institution. Axsome should not have to undertake the expense of litigating this IPR on top of the significant expense it is already bearing in the parallel DNJ Litigation, which is well into *Markman*.

II. THE ’354 PATENT

The ’354 patent issued on January 24, 2023, and claims priority to a provisional application filed on September 6, 2016. Petitioner concedes that the challenged claims are entitled to a priority date of no later than September 6, 2016. Pet. at 4.

The patent is directed to novel compositions comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride (a/k/a solriamfetol hydrochloride) and 2-chloropropane and methods of treating disorders with those novel compositions. Solriamfetol hydrochloride is a compound with the structure depicted below.



Ex. 2002 at 12.

The '354 patent and its priority applications were the first to disclose compositions comprising solriamfetol hydrochloride and *any* 2-chloropropane. Solriamfetol hydrochloride is the API in Axsome's FDA-approved Sunosi[®] drug product. The FDA approved Sunosi on March 20, 2019 (Ex. 2003 at 1), and it is indicated to improve wakefulness in adult patients with excessive daytime sleepiness ("EDS") associated with narcolepsy or obstructive sleep apnea ("OSA"). Ex. 2002 at 1. Notably, Sunosi is the first and only FDA-approved product for EDS due to OSA. Ex. 2004 at 2.

Before Sunosi was FDA approved, the patentee undertook several efforts to arrive at compositions of solriamfetol hydrochloride, but the synthesis of the API led to repeated failures. These efforts are described in Example 2 of the '354 patent. Ex. 1001 at 10:53-11:27. In short, the '354 patent identifies, for the first time, problems with the production of solriamfetol hydrochloride that resulted in either: (1) unacceptable levels of 2-chloropropane in the API; or (2) unacceptable crystals

of the API due to a thick crust forming on the reactor. *Id.* Petitioner does not contend that any of this information was in the prior art.

After these repeated failures, the inventor then solved the problems and arrived at the claimed compositions of solriamfetol hydrochloride with minimal amounts of 2-chloropropane. *See id.* at 11:28-12:19. The '354 patent discloses a “general protocol” for making the claimed compositions, as well as reaction conditions for example reactions and products. *See id.* Again, Petitioner does not contend that these synthetic conditions were in the prior art.

III. SCOPE AND CONTENT OF THE ALLEGED PRIOR ART

A. Choi268

Choi268 is U.S. Patent Application Publication No. 2005/0080268. Ex. 1006. Choi268 is cited on the face of the '354 patent, was considered by the Examiner during prosecution (Ex. 1002 at 43), and the '354 patent issued over Choi268 (Ex. 1001 at 1).

Although Choi268 discloses a preparation for solriamfetol hydrochloride (Ex. 1006 at [0068]-[0069]), there is no disclosure of any resulting product comprising 2-chloropropane (*id.*). Indeed, Choi268 does not disclose, teach, or suggest either the claimed compositions or the composition of the product resulting from the preparation of Example 1 of Choi268, much less identify specific impurities

associated with the synthesis of solriamfetol hydrochloride. In particular, Choi²⁶⁸ makes no mention of 2-chloropropane whatsoever.

B. Kaleemullah

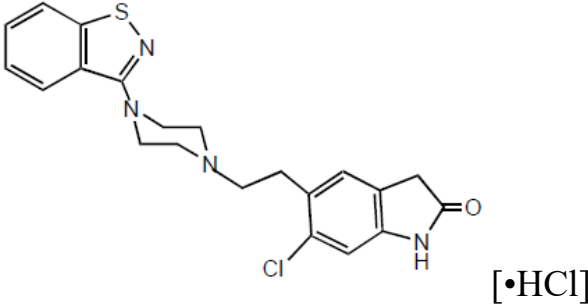
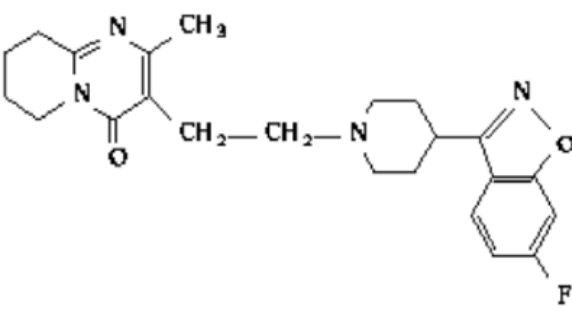
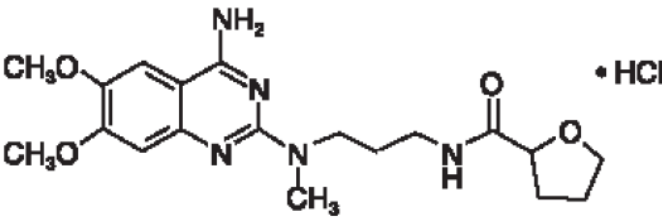
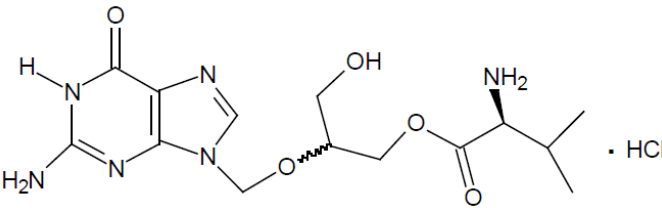
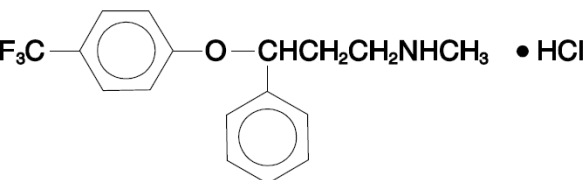
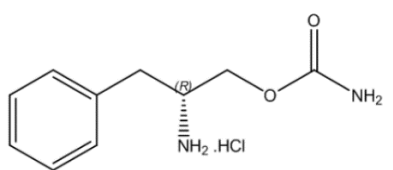
Kaleemullah is a journal article from 2011 that discusses the development and validation of a gas chromatography (“GC”) analytical method for the detection of volatile impurities in 5-(2-[4-(1,2-benzisothiazol-3-yl)-1-piperazin-1-yl] ethyl)-6-chloro-1,3-dihydro-2*H*-indol-2-one hydrochloride (“ziprasidone hydrochloride”). Ex. 1016.

Petitioner argues throughout the Petition that Kaleemullah discloses a method for detecting 2-chloropropane. *See, e.g.*, Pet. at 12. Axsome agrees. The availability of an analytical method for detecting impurities does not, however, suggest the existence of those impurities in any given product. Petitioner ignores that while the ability to detect existing impurities by analytical techniques (including GC) is routine, the experimentation that is undertaken to determine whether reaction conditions and reagents will contribute to impurities (including 2-chloropropane) in a drug substance is unpredictable and far from routine. Ex. 2001 at ¶ 27.

Kaleemullah describes using the analytical methods disclosed therein to analyze ziprasidone hydrochloride as well as several other APIs, but none are solriamfetol hydrochloride. Kaleemullah does not identify or suggest any conditions or factors that correlate to the levels or types of impurities found in each API that

was analyzed. Kaleemullah also does not disclose the synthetic processes used to make each of the analyzed APIs. And as can be seen below in Table 1, none of the APIs in Kaleemullah are structurally similar to solriamfetol hydrochloride.

Table 1: Chemical Structures of APIs

Ziprasidone HCl (See Ex. 2005 at 16)	
Risperidone (Ex. 2006 at 45)	
Alfuzosin HCl (Ex. 2007 at 8)	
Valganciclovir HCl (Ex. 2008 at 18)	
Fluoxetine HCl (Ex. 2009 at 19)	
Solriamfetol HCl (Ex. 2002 at 12)	

The above APIs have drastically different functional groups, molecular weights, number of proton donors and acceptors, number of rings. Multiple different synthetic reactions can be used to make these APIs. Kaleemullah does not disclose sufficient information to draw conclusions about which synthetic conditions or factors would result in the identification of impurities (if any) in each of the analyzed APIs, much less extrapolate its findings to other APIs that were not analyzed, such as solriamfetol hydrochloride. Ex. 2001 at ¶ 37-38.

Moreover, despite Petitioner's implication to the contrary, Kaleemullah does not disclose that 2-chloropropane will necessarily result when an API with an amine base moiety (like solriamfetol) is converted to its hydrochloride salt using HCl and IPA. Instead, and quite notably, Kaleemullah discloses the exact opposite. For the API for which the GC method was developed (ziprasidone hydrochloride), Kaleemullah discloses that the "drug substance shows *no peaks* either due to Methyl chloride, Ethyl chloride and Isopropyl chloride [a/k/a 2-chloropropane] in the sample solution. So it reveals that the drug substance highly pure [sic] and *free from alkyl chlorides* residue under investigation." Ex. 1016 at 4 (emphasis added). For the other APIs tested for 2-chloropropane and other alkyl chloride impurities (risperidone, valganciclovir hydrochloride, and fluoxetine hydrochloride), Kaleemullah likewise discloses that "[m]ost of the selected drug substance has shown *no alkyl chloride* residue." *Id.* at 8 (emphasis added). Notably, there is *no*

disclosure of 2-chloropropane, as opposed to a different alkyl chloride impurity, being present in any reaction product unless it was specifically spiked into the drug for experimental purposes. *See id.* In other words, 2-chloropropane is not a natural result, let alone a necessary result, of the synthesis of a hydrochloride salt of an amine base moiety when HCl and IPA are used. As Kaleemullah disclosed, the use of an analytical method of detection for 2-chloropropane does not suggest the existence of 2-chloropropane in tested reaction products. *See id.*; Ex. 2001 at ¶ 33.

C. Ahnaou

Ahnaou is U.S. Patent Application Publication No. 2009/0312416. Ex. 1005. A patent that issued from Ahnaou (U.S. Patent No. 9,604,917 (“the ’917 patent”), a Continuation Application from Ahnaou) is cited on the face of the ’354 patent, was considered by the Examiner during prosecution (Ex. 1002 at 43 (disclosing the ’917 patent)), and the ’354 patent issued over the ’917 patent (Ex. 1001 at 1).

Petitioner does not contend that Ahnaou discloses anything about 2-chloropropane, nor could it. Ahnaou is silent on 2-chloropropane and therefore cannot disclose, teach, or suggest a composition comprising solriamfetol hydrochloride and 2-chloropropane.

IV. INSTITUTION SHOULD BE DENIED ON THE MERITS

As explained below, Petitioner fails to establish a reasonable likelihood that it will prove that any challenged claim would have been obvious. As a result, institution should be denied.

A. Person Of Ordinary Skill In The Art

Petitioner contends that, as of September 6, 2016 (the priority date for the '354 patent), a POSA “would have had a working knowledge of pharmacology and organic chemistry art that is pertinent to the 354 Patent” and “would have had a Ph.D. in a field such as chemistry, biochemistry, medicinal chemistry, organic chemistry, analytical chemistry, pharmaceutical chemistry, pharmaceuticals, or the like,” or “[a]lternatively . . . 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.” Pet. at 4-5. For the limited purpose of this Preliminary Response, Axsome does not dispute Petitioner’s definition of a POSA.

B. Claim Construction

Petitioner asserts that no claim term requires construction. Pet. at 6-7. Axsome submits, however, that each claim should be construed to require the presence of solriamfetol hydrochloride and a minimal, *non-zero* amount of 2-chloropropane—i.e., less than about 5 ppm for all claims except claim 2, which

requires less than about 1 ppm.

In an IPR, claims terms are construed “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). “In construing claims, the analytical focus must begin and remain centered on the language of the claims themselves, for it is that language that the patentee chose to use to particularly point out and distinctly claim the subject matter which the patentee regards as his invention.” *Interactive Gift Exp., Inc. v. CompuServe Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001) (internal citations and quotations omitted). “[A]rguments made during prosecution regarding the meaning of a claim term are relevant to the interpretation of that term in every claim of the patent.” *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1579 (Fed. Cir. 1995) (affirming construction based on amendment and argument made during prosecution); *see also Sunovion Pharms. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1276-78 (Fed. Cir. 2013) (affirming construction of term consistent with how patentee used it during prosecution).

Here, the clear language of the claims, especially when combined with the clear amendment and argument made during prosecution, dictates that each claim requires a non-zero amount of 2-chloropropane. In particular, each claim recites a “composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride

and 2-chloropropane.” See, e.g., Ex. 1001 at Claim 1 (emphasis added). Therefore, based on the language of the claims alone, 2-chloropropane is a required component of the composition. See Ex. 2001 at ¶ 23.

The prosecution history solidifies Axsome’s position. Applicant made a preliminary amendment to claim 20 (now claim 1) to require the presence of 2-chloropropane (adding the “and 2-chloropropane” requirement):

20. (Currently Amended) A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride and 2-chloropropane, wherein the composition comprises ~~comprising~~ less than about 5 ppm 2-chloropropane.

Ex. 1002 at 14. During prosecution, in response to an Office action rejecting then claim 20, the applicant distinguished the prior art by arguing that “the composition of present claim 20 *requires the presence of 2-CP* (‘A composition comprising (R)-2-amino-3-phenylpropyl carbamate hydrochloride *and 2-chloropropane*’), albeit in an amount less than 5 ppm.” *Id.* at 719 (emphasis added). The prior art, on the other hand, did not disclose a composition with any 2-chloropropane. *Id.* For these reasons, Axsome’s proposed construction should be adopted.

C. The Challenged Claims Would Not Have Been Obvious Over Choi²⁶⁸ In View Of Kaleemullah And Ahnaou (Ground 1)

As explained below, there are multiple fatal flaws to Petitioner’s Ground 1, any (and all) of which are sufficient to deny institution.

1. The asserted art does not disclose, teach, or suggest 2-chloropropane as an impurity in solriamfetol hydrochloride and there was therefore no known problem to be solved

Under Federal Circuit law, an obviousness analysis first requires “determining that claimed elements are present in the prior art.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). Where the art does not recognize a problem to be solved, the “invention can often be the recognition of a problem itself.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013). That is because, without knowledge of a problem to be solved, a POSA would have had no motivation to arrive at the claimed inventive solution. *See Novartis Pharms. Corp. v. Watson Lab’ys, Inc.*, 611 F. App’x 988, 995 (Fed. Cir. 2015) (“Even an obvious solution, however, does not render an invention obvious if the problem solved was previously unknown.”); *see also Leo Pharm.*, 726 F.3d at 1356-57 (reversing obviousness finding where the prior art did not recognize the problem to be solved by the claimed invention and, thus, a POSA would not have had a reason to attempt to modify or improve upon the prior art in the first place).

Here, the asserted art does not disclose 2-chloropropane as an impurity in solriamfetol hydrochloride, or even in APIs with amine base moieties generally. Without knowledge that 2-chloropropane was a genotoxic impurity present in solriamfetol hydrochloride, a POSA would have had no motivation to attempt to

arrive at a composition with solriamfetol hydrochloride and a minimal amount of 2-chloropropane. Petitioner's arguments to the contrary lack any factual support.

a. 2-chloropropane was not known to be an impurity in solriamfetol hydrochloride

Petitioner relies on a single organic synthesis of solriamfetol hydrochloride that uses “both HCl and isopropanol as reagents during salt precipitation” to imply that 2-chloropropane “would be formed.” Pet. at 10, 12, 19. Petitioner relies solely upon Choi268 for the disclosure of a solriamfetol hydrochloride synthesis but admits that “Choi268 does not *expressly* disclose the formation of ‘2-chloropropane.’” Pet. at 10 (emphasis added).²

² Notably, nowhere does Petitioner argue, let alone present any evidence, that the formation of 2-chloropropane is inherent in Choi268. “To establish that a prior art reference inherently—rather than expressly—discloses a claim limitation, ‘the limitation at issue necessarily must be present, or [is] the natural result of the combination of elements explicitly disclosed by the prior art.’” *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018) (quoting *Par Pharm.*, 773 F.3d at 1196). “[I]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of

Because Choi268 is entirely silent on 2-chloropropane, Petitioner claims that 2-chloropropane “would be formed” in the Choi268 synthesis in view of the disclosure in Kaleemullah. Pet. at 10, 12. But as explained above, Kaleemullah does not disclose solriamfetol or solriamfetol hydrochloride. Instead, Kaleemullah investigates the impurities in other APIs that Petitioner does not even attempt to establish have any correlated or similar properties to solriamfetol hydrochloride. See *supra* at III.B. Thus, a POSA would not have had any reason to believe that the disclosures of Kaleemullah would be applicable to solriamfetol hydrochloride.

But even if one were to assume that the disclosures of Kaleemullah could be applicable to solriamfetol hydrochloride (which there is no support for), Kaleemullah’s disclosures directly contradict Petitioner’s argument. Petitioner incorrectly equates Kaleemullah’s purported disclosure that “treating ziprasidone base ‘in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid’ results in the formation of ‘[i]sopropyl chloride,’” to an “*express* disclosure of the formation of ‘2-chloropropane’ during salt precipitation with HCl and isopropanol.” Pet. at 10 (emphasis added), *see also id.* at 11-12, 24-25. Petitioner is wrong.

circumstances is not sufficient.” *Id.* (quotations and internal citations omitted)

(emphasis in original). Petitioner did not even try to meet this high burden.

Kaleemullah clearly states that, when using the analytical methods disclosed therein, “[t]he drug substance [i.e., ziprasidone hydrochloride] shows *no peaks* either due to Methyl chloride, Ethyl chloride and Isopropyl chloride in the sample solution” revealing that the synthesized drug substance was “*free from alkyl chloride[]* residue under investigation.” Ex. 1016 at 4 (emphasis added). In other words, the ziprasidone salt form was tested using the disclosed analytical methods and no 2-chloropropane was detected. Accordingly, Kaleemullah is not an “express disclosure”—or any disclosure—of the formation of 2-chloropropane in ziprasidone hydrochloride. Ex. 2001 at ¶¶ 26, 34.

In addition to ziprasidone hydrochloride, Kaleemullah describes several other APIs—risperidone, valganciclovir hydrochloride, and fluoxetine hydrochloride—that were also tested for 2-chloropropane (among other impurities). *Id.* at 8-9. While Kaleemullah does not disclose the specific conditions for synthesis of any of these drug substances, Kaleemullah does disclose that “most of the selected drug substance has shown *no alkyl chloride* residue during the analysis even though precipitation step uses hydrochloric acid treatment for their respective alcoholic drug base,” meaning that “[t]he *absence of alkyl chloride* residue in the drug confirms the complete precipitation step, leads to no un-reacted alcoholic moiety in the drug matrix.” *Id.* at 8 (emphasis added); *see also id.* at Table 4 (disclosing no significant difference between the spiked amounts of alkyl chloride impurity and the amount

recovered). Indeed, there is *no* disclosure of 2-chloropropane being present in any reaction product unless it was specifically spiked into the drug for experimental purposes. *See id.*; Ex. 2001 at ¶ 34.

Therefore, if Kaleemullah teaches anything, it is that for all of its disclosed APIs that include a precipitation step using HCl and an alcohol (e.g., isopropanol, ethanol, methanol), none resulted in an alkyl chloride impurity.³ Simply put,

³ While incorrect about Kaleemullah's disclosure, Petitioner contends that the alleged disclosures are "consistent with Patent Owners' statement during prosecution that '[2-chloropropane] is the product of the reaction between isopropanol and HCl.'" Pet. at 31 (quoting Ex. 1003 ¶ 86). That post-priority statement, however, is not prior art and is based on work disclosed for the first time in the '354 patent specification. Reliance on it would be legal error. *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (finding the lower court improperly "used the invention to define the problem that the invention solves"); *Ecolchem, Inc. v. S. Cali. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) ("[D]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness") (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 880 (Fed. Cir. 1998).

Kaleemullah does not disclose, teach, or suggest that 2-chloropropane would be present in an organic synthesis using HCl and IPA for any API, let alone be present in solriamfetol hydrochloride, including solriamfetol hydrochloride synthesized according to Choi268.

b. With no known problem, there would have been no motivation to even attempt to arrive at the claimed inventions

Petitioner's subsequent reliance on references purportedly motivating a POSA to reduce levels of impurities in APIs as a general proposition is a red herring.⁴ Without knowledge of 2-chloropropane being an impurity in solriamfetol hydrochloride, there would have been no known problem, and a POSA would have

⁴ While Petitioner relies on Kaleemullah for this argument (*see e.g.*, Pet. at 13 (“residual impurities should be controlled”)), it also discusses Callis (Ex. 1017) (*see, e.g.*, Pet. at 13 n.4 (“genotoxic impurity (GTI) limits”), 15 (“ALARP principle”)), Liu (Ex. 1014) (*see e.g.*, Pet. at 14 (“(GTI)s in pharmaceuticals at trace levels”)), Cimarosti (Ex. 1015) (*see, e.g.*, Pet. (“methods to measure trace levels of genotoxic impurities”)), Kim (Ex. 1007) (*see, e.g.*, Pet. at 14-15 (“trace amounts of a genotoxin”)), EMEA guidelines (*see e.g., id.* at 15 (“ALARP principle”)), and Yang (Ex. 1019) (*see e.g.*, Pet. at 19-20 (“reduce genotoxic impurities”)).

had no motivation to even attempt to reduce levels of 2-chloropropane and arrive at the claimed minimal-impurity compositions.

Both *Novartis* and *Leo Pharmaceutical* are factually on-point and instructive. In *Novartis*, the claimed inventions covered pharmaceutical formulations comprising an active ingredient (rivastigmine) and an antioxidant. 611 F. App'x at 991. The district court found that the prior art “collectively . . . disclosed pharmaceutical compositions comprising rivastigmine and an antioxidant,” but that “rivastigmine was not known to be susceptible to oxidative degradation at the time of the invention, and that the cited prior art did not teach otherwise.” *Id.* at 992. “Thus, [the district court] held [that] it would not have been obvious to add an antioxidant to a rivastigmine composition in a transdermal device.” *Id.* The Federal Circuit affirmed, finding that the district court “did not clearly err in finding that the prior art does not unambiguously identify oxidative degradation to be a known problem with rivastigmine, and that therefore one of skill would not have had a reason to add an antioxidant to the [prior art] formulation.” *Id.* at 995-96.

The same is true here. Without any knowledge that 2-chloropropane would be an impurity in solriamfetol hydrochloride, there would have been no reason to consult any prior art to attempt to minimize the level of that impurity in solriamfetol hydrochloride.

Leo Pharmaceutical is likewise analogous. There, the claimed inventions were directed to “a pharmaceutical composition comprising three components: a category A component (vitamin D analog); a category B component (corticosteroid); and a category C solvent” to address and to solve a storage stability problem with such ingredients. 726 F.3d at 1349. The U.S. Patent and Trademark Office, during reexamination proceedings, found that the claimed inventions would have been obvious based on a combination of prior art references, which disclosed all elements of the claims. *See id.* at 1350-51. The Federal Circuit reversed that obviousness finding because the prior art did not “recogniz[e] or solv[e] the storage stability problems associated with the combination.” *Id.* at 1353. And “because neither [prior art reference] recognized or disclosed the stability problem, the record show[ed] no reason for one of ordinary skill in the art to attempt to improve upon [the prior art formulations].” *Id.* at 1354. The Federal Circuit, in reversing the obviousness finding, specifically held that, “[o]nly after recognizing the existence of the problem would an artisan *then* turn to the prior art and attempt to develop a new formulation for storage stability.” *Id.* (emphasis original). In other words, without a known problem to be solved, there would be no reason to consult the prior art at the time of invention in the first place. *See id.*

Similarly again, here, without any knowledge that 2-chloropropane would be an impurity in solriamfetol hydrochloride, there would have been no reason to

consult any prior art to attempt to minimize the level of that impurity in solriamfetol hydrochloride. Petitioner's argument otherwise is deeply rooted in hindsight and the '354 patent itself. But the "fact finder must not allow its analysis to be distorted by hind-sight bias." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019). Indeed, Petitioner cannot "use the challenged patent as a roadmap to reconstruct the claimed invention using disparate elements from the prior art." *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019). Petitioner's argument, committing this exact legal error, should be rejected.

2. If there was a known problem, it would have taught away from, or at the very least not have motivated a POSA to arrive at, a composition with any 2-chloropropane

"[I]n determining obviousness, the challenger bears the burden of establishing that a skilled artisan would have been motivated to combine the teachings of the prior art references *to achieve the claimed invention. . . .*" *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017) (emphasis added) (internal citation and quotations omitted). The Federal Circuit has repeatedly held that the prior art teaches away when it describes claimed features "as potentially harmful," *Cordis Corp. v. Bos. Sci. Corp.*, 561 F.3d 1319, 1332 (Fed. Cir. 2009), or where they could "exhibit[] negative effects, such as toxicity," *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1358 (Fed. Cir. 2007). Further, "even if [the prior art] is not found to teach away, its statements regarding preferences are relevant

to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference.” *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018).

Here, the claims require a non-zero amount of 2-chloropropane. *See supra* at IV.B. Petitioner has alleged that 2-chloropropane is a genotoxic impurity. *See, e.g.*, Pet. at 12. Even if one were to accept Petitioner’s argument that a POSA would have understood the conversion of solriamfetol to solriamfetol hydrochloride in the presence of HCl and IPA would result in 2-chloropropane (which there is no support for), Petitioner never explains why a POSA would then continue to use IPA in the face of forming a genotoxic impurity. A POSA would have understood that the IPA is not necessary to form the hydrochloride salt. Ex. 2001 at ¶ 41. Indeed, the prior art discloses that for solriamfetol specifically, the hydrochloride salt could be made with several solvents, the bulk of which are non-alcohol solvents, including “an ethereal solvent such as THF, an alcoholic solvent such as methanol, an ester solvent such as ethyl acetate, an aromatic solvent or any compositional mixture thereof.” Ex. 2010 at 4:43-5:37. The prior art likewise discloses an alternative solvent for the API that Petitioner relies on from Kaleemullah. *See* Ex. 2011 at Example 16 (disclosing the use of diethyl ether in the synthesis of ziprasidone hydrochloride).

Petitioner does not address any of the alternative solvents, nor does Petitioner (or its expert) explain why a POSA would continue to use IPA and risk forming (in

Petitioner's view) the genotoxic impurity, 2-chloropropane. Under Federal Circuit law, the risk of the genotoxic impurity would have taught away from, or at the very least not have motivated a POSA to arrive at, the specifically claimed inventions, which all require a non-zero amount of 2-chloropropane. *See Cordis*, 561 F.3d at 1332 (affirming denial of judgment of a matter of law for obviousness where prior art lacked motivation and taught away from modification when the element was “potentially harmful”); *Takeda*, 492 F.3d at 1358-60 (affirming lack of motivation finding where prior art taught the alleged starting material in the reaction had toxicity issues); *Polaris*, 882 F.3d at 1069-70 (vacating Board of Patent Appeals and Interferences' decision and remanding with the direction that “[e]ven if the Board determines that [the prior art] does not teach away because it merely expresses a general preference, the statements in [the prior art] are still relevant to determining whether a skilled artisan would be motivated to combine [the prior art]”).

3. Petitioner fails to demonstrate a reasonable expectation of success in arriving at the claimed minimal-impurity solriamfetol hydrochloride compositions

For the prior art to render an invention obvious, it must also lead to a “reasonable expectation of success” in arriving at the claimed inventions. *Millennium Pharm*, 862 F.3d at 1366 (internal citation omitted). “The reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention.” *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021); *see also Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965-66 (Fed. Cir. 2014) (“[F]ailure to consider the appropriate scope of the . . . claimed invention in evaluating the reasonable expectation of success . . . constitutes a legal error. . . .”). “To the extent an art is unpredictable, as the chemical arts often are,” proving a reasonable expectation of success is a “difficult hurdle because potential solutions are less likely to be genuinely predictable.” *Eisai Co. Ltd. v. Dr. Reddy’s Lab’s, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *see also HZNP Meds. LLC v. Actavis Laby’s UT, Inc.*, 940 F.3d 680, 703 (Fed. Cir. 2019) (affirming nonobviousness where “the components of the inventive formulation, interact in an unpredictable or unexpected way, such that the results emanating into [the claimed formulation] were not obvious”).

The Petition alleges a single theory for a reasonable expectation of success in arriving at the claimed inventions in two places. Both generally state:

[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”).

Pet. at 19-20, *see also id.* at 36-37 (same). Petitioner’s expert parrots the same conclusory alleged reasonable expectation of success. *See* Ex. 1003 at ¶¶ 64, 98. Both the Petition and Petitioner’s expert, however, never explain *why* a POSA would have reasonably expected “routine experimentation” to successfully result in the claimed minimal-impurity solriamfetol hydrochloride compositions. The lack of factual support for a reasonable expectation of success precludes institution.

Moreover, the existence of repeated failures leading to the claimed inventions, which are documented in the '354 patent, further solidifies a lack of reasonable expectation of success.

a. Petitioner's "routine experimentation" theory is unsupported by the asserted art

The Federal Circuit has explained that any "reference to 'routine testing' or 'routine experimentation' is disfavored" and is only "appropriate" where the prior art "predicted the results, which [the patentee] merely had to verify through routine testing." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) (finding reasonable expectation of success where there was only one parameter to vary (the anion salt), the salt was expected to be successful, and a routine test was used to verify success). But "[a] solution is not obvious simply because it was obvious to conduct experiments to try to solve the problem." *Vanda Pharms. Inc. v. Roxane Laby's, Inc.*, 203 F. Supp. 3d 412, 427 (D. Del. 2016) (finding no reasonable expectation of success when the results of a study suggested by the prior art were "impossible to predict"), *aff'd sub nom. Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018); *see also Leo Pharm.*, 726 F.3d at 1357 (rejecting routine experimentation theory where "there [wa]s no indication in the prior art which of these possible formulations would be the most promising to try").

The Petition and Petitioner's expert cite two references to allegedly show "routine experimentation" here. Neither reference, however, has anything to do with

solriamfetol hydrochloride, nor do they reflect or comment on the reaction conditions Petitioner alleges are relevant to Choi268. Ex. 2001 at ¶¶ 37-38, 43. Petitioner offers no evidence to the contrary.

Petitioner cites to Yang (Ex. 1019) as “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, e.g. Pet. at 19-20 (quoting Ex. 1019 at 5). But the “solution[.]” used in Choi268 is not “methanolic.” In other words, the only synthetic process for solriamfetol hydrochloride relied on by Petitioner does not use methanol. Instead, it uses isopropyl alcohol (a/k/a IPA), as the Petition admits. See, e.g., *id.* at 7; Ex. 2001 at ¶ 43. Petitioner and its expert offer no argument, let alone evidence, that the reaction parameters for methanolic solutions would be the same for non-methanolic solutions or that finding these reaction parameters would be routine. Also, there is nothing tying the 10 °C in Yang (Ex. 1019) or the unspecified reaction conditions in Kim (Ex. 1007) to any reaction of solriamfetol hydrochloride, let alone anything that would permit the predictability of such a reaction. Ex. 2001 at ¶ 43. In short, the proposed reaction conditions cannot be routine because they fail to identify how they can be applied to modify the specific reaction conditions for solriamfetol hydrochloride. Ex. 2001 at ¶ 44.

Moreover, unlike the one reaction variable in *Pfizer*, the two quotes that

Petitioner relies upon from Yang and Kim already disclose at least five variables (solvent type, temperature, acid concentration, acid exposure time, and the addition of water) that need to be considered during the alleged “routine experimentation” that Petitioner claims would lead from Choi268 to the claimed inventions. Ex. 2001 at ¶ 44. The actual synthetic experimental disclosure in Choi268 itself adds several more variables to alter the final product. *Id.* at ¶ 44-45. Choi268 discloses varying starting materials; solvents and reagents used in the synthesis such as dichloromethane, 20% aqueous solution of sodium hydroxide, brine, sodium sulfate, isopropanol, 6.5M HCl solution (in isopropanol), and acetone; and additional steps in the reaction that allow for variability, for example (a) “[t]he mixture was stirred,” but no stir rate is provided; (b) “methanesulfonic acid . . . was slowly added,” but no time frame is provided; (c) “[t]he ice-bath was removed and the reaction mixture was stirred until D-phenylalaninol was no longer detected” then “80 grams of ice was added and the reaction mixture was cooled in an ice bath,” but no temperature or time was provided for the removal of the ice bath; (d) “concentrated in vacuo,” but no technique, equipment, or parameters were provided; (e) “crude reaction product . . . was transferred to a three-neck round bottom flask equipped with a mechanical stirrer,” but does not say to stir mixture or at what rate; (f) “HCl solution was slowly added,” but no time frame is provided; (g) “660 mL of acetone was added,” but fails to disclose the rate of addition or the temperature of the acetone;

(h) “product was washed thoroughly,” but fails to disclose specific technique and duration; (i) “ice-chilled isopropanol-acetone,” but fails to disclose temperature; (j) “dried in vacuo,” but fails to provide equipment and temperature. Ex. 1006 at [0068]-[0069]; Ex. 2001 at ¶ 44.

Even setting aside whether altering these various parameters is routine, Petitioner never addresses these variables or how any (or all) would be combined to allegedly reasonably lead to the claimed compositions. Petitioner also does not identify anything to support its argument that the result of changing a particular variable would achieve a reasonably predictable result. All that Petitioner and its expert say is “routine experimentation” without any explanation or analysis. That unsupported attorney argument and conclusory expert testimony cannot support a finding of obviousness under Federal Circuit law. *See, e.g., TQ Delta*, 942 F.3d at 1358, 1363 (reversing IPR obviousness finding because “[c]onclusory expert testimony does not qualify as substantial evidence”). *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009) (noting “attorney argument . . . is not evidence”). In sum, the facts here are a far cry from the “particularized facts” permitting for application of the “routine experimentation” argument in *Pfizer*. *See* 480 F.3d at 1367 (emphasis original).

b. Repeated failures further evidence the lack of a reasonable expectation of success

“The Federal Circuit has frequently focused on the unsuccessful attempts of

the patentee in its obviousness analyses.” *Pfizer Inc. v. Teva Pharms. USA, Inc.*, No. 04-754, 2006 WL 8457596, at *1-2 (D.N.J. Oct. 13, 2006) (internal citation omitted) (permitting evidence on patentee’s own failures); *see also, e.g., Micro Chem. v. Great Plains Chem.*, 103 F.3d 1538, 1547 (Fed. Cir. 1997), *abrogated on other grounds by EZ Dock, Inc. v. Schafer Sys.*, 276 F.3d 1347 (Fed. Cir. 2002) (patentee’s failed research efforts evidenced that a POSA would not have had a reasonable expectation of success); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (holding that “years of research [by the patentee] that preceded the claimed invention” showed that “[t]he evidence as a whole d[id] not support the PTO’s conclusion that the claimed invention would have been obvious”); *Syntex (U.S.A.) LLC v. Apotex Inc.*, No. 01-2214, 2006 WL 1530101, at *27 (N.D. Cal. June 2, 2006) (“The fact that Syntex scientists tried unsuccessfully for several years to formulate [the claimed inventions] using other surfactants and ingredients suggests that the inventions . . . were not obvious.”).

Here, Petitioner’s inability to articulate a reasonable expectation of success is exacerbated by the existence of evidence of unpredictability in the ’354 patent itself. The ’354 patent discloses for the first time that, before the claimed inventions, there were repeated efforts to formulate solriamfetol hydrochloride with minimal levels of 2-chloropropane, but failure, instead of success, was achieved each time. *See Ex. 1001 at 10:53-11:27.* These failures involved, among other variable parameters,

drying at elevated temperatures, reslurrying the crystals, changing solvents, and charging HCl gas at different temperatures. *See id.*; Ex. 2001 at ¶ 47. Ultimately, the inventors needed to change multiple variables to obtain an acceptable product in the exemplary reaction that had reduced levels of 2-chloropropane including: reducing the reaction temperature to 20-30 °C, using a 37% aqueous solution of HCl (rather than gas that supersaturated the solution), slowly charging HCl to the reaction mixture, stirring the clear solution for 15 minutes after seeding (rather than stirring the already crystallized solution), adding a second charge of 37% aqueous solution of HCl to the reaction mixture, stirring the reaction mixture for 1 hour, then cooling it to -15 °C in 2 hours (rather than 40 °C, then 20 °C, then 3 °C over 12 hours), and finally adding a drying step at 35 °C under dry nitrogen stream (rather than drying at room temperature at reduced pressure). *See* Ex. 1001 at 11:28-52; Ex. 2001 at ¶ 47.

All of these different variables and different outcomes are contrary to Petitioner's "routine experimentation" reasonable expectation of success argument. They, instead, support experimentation being unpredictable. In short, without the guidance provided in the '354 patent, a POSA would have no guidance or direction to arrive at the claimed minimal-impurity solriamfetol hydrochloride compositions. Ex. 2001 at ¶ 48. Where, like here, a patent challenger "urges an obviousness finding by merely throw[ing] metaphorical darts at a board in hopes of arriving at a

successful result, but the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, courts should reject hindsight claims of obviousness.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (rejecting “routine experimentation” theory and reversing obviousness because lack of reasonable expectation of success) (internal citation and quotation marks omitted).

* * *

For the foregoing reasons, the Petition should be denied on the merits.

V. INSTITUTION SHOULD BE DENIED UNDER SECTION 314(a)

Discretionary denial is also warranted under 35 U.S.C. § 314(a) because the validity of the '354 patent is being litigated concurrently in a parallel DNJ Litigation. *See generally Axsome Malta Ltd., et al. v. Alkem Laby's Ltd., et al.*, No. 23-20354 (MDA)(LDW) (D.N.J.). The DNJ Litigation has been ongoing since September 13, 2023, when Axsome filed a Complaint against Petitioner and other defense groups, accusing Petitioner (and those defense groups) of infringing patents, including the '354 patent. Ex. 2012 at 72-73, 34-35, 45-46, 58-59, 85-86, 98-100. Petitioner waited until the last possible moment to file this Petition challenging the '354 patent that had already been actively in suit for over a year and half. Ex. 2013 at 1. In its Petition, Petitioner relies on references and theories that it has already identified in

the contentions it served in the DNJ Litigation. Ex. 2014; Ex. 2001 at ¶ 30.

Under Section 314(a), the Board may deny institution when there is a parallel, co-pending proceeding related to the same patent using the factors delineated in *Apple Inc. v. Fintiv, Inc.*: (1) whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted; (2) proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision; (3) investment in the parallel proceeding by the court and the parties; (4) overlap between issues raised in the petition and in the parallel proceeding; (5) whether the petitioner and the defendant in the parallel proceeding are the same party; and (6) other circumstances that impact the Board’s exercise of discretion, including the merits. IPR2020-00019, Paper 11 at 5-6 (PTAB Mar. 20, 2020). The “Board takes a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Id.* at 6. Here, the *Fintiv* factors weigh strongly against institution in view of the DNJ Litigation.

A. Factors 1 And 2. The Unlikelihood Of A Stay And The Proximity Of Trial Date To The Final Written Decision Warrant Denial of Institution

The absence of a stay and the proximity of the projected trial date in the DNJ Litigation to a Final Written Decision favor denial of institution.

There is no stay in the DNJ Litigation; Petitioner has not requested a stay and Axsome has no intention of seeking one. A stay would be unlikely even if requested

because there is no reason to assume that any of the three other defense groups who are currently parties to the DNJ Litigation would be amenable to a stay. Moreover, there are 29 other patents-in-suit and to Axsome's knowledge, the presiding judges have never granted an opposed motion to stay proceedings pending *inter partes* review, let alone when only 1 of 30 patents is challenged in an IPR. On the other hand, judges in the District of New Jersey have denied motions to stay under similar circumstances. *See, e.g., Bausch Lomb Inc., et al. v. Slayback Pharma LLC, et al.*, No. 21-16766 (RK)(RLS), Dkt No. 75 at 1 (D.N.J. Feb. 10, 2023); *Gesture Tech. Partners, LLC v. LC Elecs. Inc., et al.*, No. 21-19234 (JMV) (MAH), Dkt. No. 58 at 3 (D.N.J. Jan. 18, 2023); *Horizon Pharma, Inc., et al. v. Dr. Reddy's Laby's, Inc. et al.*, No. 15-3324 (SRC), Dkt No. 117 at 4 (D.N.J. July 25, 2018).

Without a stay and under the current schedule, the projected trial date for the DNJ Litigation would be close to a Final Written Decision here. Under the statutory deadlines, an institution decision is expected late April 2025 and, if an *inter partes* review is instituted, a Final Written Decision would be expected late April 2026. *See* 35 U.S.C. §§ 314, 316. The DNJ Litigation has a projected trial date in Q2 2026. The litigation is under the framework of the Hatch-Waxman Act, which prohibits each of the defense groups from launching their generic solriamfetol oral tablet drug products until after the expiration of the 30-month stay in December 2026. The parties to the DNJ Litigation, including Axsome and Petitioner, have negotiated

several times over the last year so that the scheduling order enables entry of a final judgment in the case before the 30-month date. Ex. 1013 at 6. Under the current schedule, trial in the DNJ Litigation is projected to occur in Q2 2026, at least six months before the expiration of the 30-month stay, consistent with the negotiations among the parties and with other Hatch-Waxman actions in the District of New Jersey.⁵ See, e.g., *Merck Sharp & Dohme Corp. v. Actavis Laby's FL, Inc., et al.*, No. 15-6075, Dkt No. 87 (D.N.J. Dec. 14, 2016); *Teva Neuroscience, Inc., et. al. v. Watson Pharma, Inc., et. al.*, No. 10-5078, Dkt No. 417 (D.N.J. Jan. 2, 2013); *Boehringer Ingelheim Pharms. Inc., et al. v. Dr. Reddy's Laby's, Ltd. et al.*, No. 16-2394, Dkt. No. 11 (D.N.J. May 13, 2016); *TherapeuticsMD, Inc. v. Teva Pharms. USA, Inc. et al.*, No. 20-3485, Dkt. No. 51 (D.N.J. Dec. 19, 2020); see also *Takeda Pharm. Co. Ltd., et al. v. Norwich Pharms., Inc., et al.*, No. 20-8966, Dkt. No. 318 (D.N.J. July 14, 2022).

⁵ Petitioner argues that “in the District Court of New Jersey, the median time from filing to trial was 57.8 months” and thus “trial can be expected in approximately July 2028.” Pet. at 58. This median is not representative of the trial schedule in Hatch-Waxman cases as distinct from other civil litigations in the district. Nor does it reflect the current operative case schedule for the DNJ Litigation.

Because a stay is extremely unlikely and because of the proximity of the dates projected for trial in the DNJ Litigation and the Board's Final Written Decision, going forward in this proceeding would be unnecessarily duplicative and burdensome. As such, Factors 1 and 2 strongly weigh in favor of discretionary denial. *See Fintiv*, IPR2020-00019, Paper 11 at 6-8; *see also Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 15 (PTAB Dec. 1, 2020) (precedential as to § II.A).

B. Factor 3. The Petitioner's Delay In Filing The Petition and The Parties' And The Court's Investment Of Resources In The Parallel Proceeding Warrant Denial of Institution

Petitioner's delay in filing its Petition for *inter partes* review and the substantial investment of resources (to date and anticipated) in the DNJ Litigation also strongly weigh in favor of discretionary denial.

The DNJ Litigation has been pending for over a year and half and the parties have already expended significant resources litigating the '354 patent, including the exchange of discovery requests, production of documents, and the preparation and exchange of thousands of pages of infringement and validity contentions. By June 2024 in the DNJ Litigation, Petitioner had served its initial disclosures and non-infringement and invalidity contentions to Axsome as to the '354 patent. Yet, Petitioner waited six months after that, until the very last day of the statutory deadline, to file its Petition. Ex. 2013 at 1. To date, Axsome has produced

documents and served validity contentions that respond to Petitioner's invalidity contentions and supplemental invalidity contentions, which identify over 85 alleged prior art references, including the Choi²⁶⁸ and Ahnaou references cited in the Petition.

By the time the Board makes an institution decision here, the parties to the DNJ Litigation and the district court will have expended even more time and resources on additional discovery and claim construction, with opening *Markman* briefs to be served, expert *Markman* discovery substantially completed, and a *Markman* hearing to be scheduled prior to the expected date of the institution decision. Ex. 1013. The Board has denied institution in similarly situated cases based on this factor. See *10X Genomics v. President & Fellows of Harvard Coll.*, IPR2023-01299, Paper 15 at 18 (PTAB Mar. 7, 2024); *Samsung Elecs. Co. v. Mojo Mobility Inc.*, IPR2023-01098, Paper 11 at 8-9 (PTAB Feb. 9, 2024); *Samsung Elecs. Co., Ltd. et al v. Ancora Techs., Inc.*, IPR2020-01184, Paper 11 at 18 (PTAB Jan. 5, 2021); *Mylan Laby's Ltd. v. Janssen Pharms.*, IPR2020-00440, Paper 17 at 18-19 (PTAB Sept. 16, 2020).

Petitioner's delay, especially in view of the magnitude of the work already done in the parallel DNJ Litigation, strongly supports a discretionary denial under Factor 3 to avoid duplication and burden on the court, the U.S. Patent and Trademark Office, and Axsome.

C. Factors 4 and 5. The Same Parties And Issues In The Petition And Parallel DNJ Litigation Warrant Denial Of Institution

The parties to the Petition and parallel DNJ Litigation are the same, litigating the same claims, asserting the same theories, and using substantially the same references. This overlap strongly favors denial of institution.

Axsome and Petitioner are plaintiffs and one of the defense groups in the parallel DNJ Litigation, respectively. In the Petition, Petitioner challenges claims 1-8 of the '354 patent. In the parallel DNJ Litigation, Petitioner challenges claims 1-7 of the '354 patent. Petitioner does not argue that “the non-overlapping claims differ significantly in some way.” *Fintiv*, IPR2020-0019, Paper 11 at 13 n.25. Nor has Petitioner sought a *Sotera* stipulation stating it would “not pursue any ground raised or that could have been reasonably raised.” *See Sotera*, IPR2020-01019, Paper 12 at 14.

In the Petition, Petitioner relies on a combination of Choi268, Ahnaou, and Kaleemullah to contend that claims 1-8 of the '354 patent are invalid as obvious. In the DNJ Litigation, Petitioner relies on a combination of Choi268, Ahnaou, and Kim to contend that claims 1-7 of the '354 patent are invalid as obvious. Ex. 2014 at 11. Therefore, Petitioner’s obviousness theories in both the DNJ Litigation and Petition rely on the same two references – Choi268 and Ahnaou. Moreover, the theories are the same because in its Petition, Petitioner relies on Kaleemullah for its contention that formulations comprising 2-chloropropane were known in the art and that a

POSA would want to minimize that alleged impurity (*see, e.g.*, Pet. at 10), and in the DNJ Litigation, Petitioner contends that Kim discloses the same (Ex. 2014 at 11). The disclosures of Kaleemullah and Kim are cumulative (Ex. 2001 at ¶ 30), and the obviousness theories are the same notwithstanding which one is combined with Choi268 and Ahnaou. Petitioner does not dispute that, because Kaleemullah is cumulative of Kim, there is substantial overlap in the theories and prior art references in the DNJ Litigation and its Petition. *See* Pet. at 59.

Under *Fintiv*, denial of institution is favored where the “petition includes the same or substantially the same claims, grounds, arguments, and evidence as presented in the parallel proceeding.” IPR2020-00019, Paper 11, at 12; *see also Mylan Laby’s*, IPR2020-00440, Paper 17 at 21. Likewise, denial is favored where the parties are the same.⁶ *See 10X Genomics*, IRP2023-01299, Paper 15 at 20; *Mojo*

⁶ Petitioner incorrectly argues that “Factor 5 is neutral” because “*Fintiv* ‘says nothing about situations in which the petitioner is the same as, or is related to, the district court defendant.’” Pet. at 59-60 (internal citation and quotations omitted). Even if *Fintiv* “says nothing,” subsequent precedential PTAB authority makes clear that where the petitioner and defendant in the parallel proceeding are the same party, Factor 5 favors denial. *See Sotera*, IPR2020-01019, Paper 12 at 19 (citing *Fintiv*,

Mobility, IPR2023-01098, Paper 11 at 13.

The overlap in parties and issues across the Petition and the parallel DNJ Litigation strongly supports discretionary denial of institution under Factors 4 and 5 to avoid duplication and burden to the court, the Patent Office, and Axsome.

D. Factor 6. Other Factors Warrant Denial of Institution

Since Factors 1-5 favor discretionary denial, under *CommScope Technologies LLC v. Dali Wireless, Inc.*, the Board must also consider whether the Petition presents compelling merits. IPR2022-01242, Paper 23 at 4-5 (PTAB Feb. 27, 2023); *see also* PTAB Consolidated Trial Practice Guide, November 2019 at 3-5. For the reasons discussed above (*see supra* at IV), it does not. Because the Petition fails to present compelling merits and *Fintiv* Factors 1-5 heavily favor discretionary denial, the Board can, and should alternatively, deny institution under 35 U.S.C. § 314(a).

VI. CONCLUSION

For the reasons set forth above, Petitioners have failed to establish a reasonable likelihood of prevailing as to any challenged claim, and the Board should deny institution. Alternatively, institution should be denied under 35 U.S.C. § 314(a).

IPR2020-00019, Paper 11 at 13-14).

Date: January 23, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Patent Owner Preliminary Response complies with the applicable type-volume limitations of 37 C.F.R. § 42.24 (b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Preliminary Response, including footnotes, contains 9211 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(i).

Date: January 23, 2025

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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

CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certify that PATENT OWNER PRELIMINARY RESPONSE PURSUANT TO 35 U.S.C. § 313 AND 37 C.F.R. § 42.107 and accompanying exhibits (Exs. 2001-2021) were served on January 23, 2025 by filing these documents through the Patent Review Processing System, as well as e-mailing copies to sborder@winston.com and jwong@winston.com.

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