

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

**DECLARATION OF DR. LEONARD J. CHYALL,
IN SUPPORT OF PATENT OWNER PRELIMINARY RESPONSE
PURSUANT TO 35 U.S.C. § 313 AND 37 C.F.R. § 42.107**

I, Leonard J. Chyall, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Patent Owners SK Biopharmaceuticals Co., Ltd. and Axsome Malta Ltd. (“Axsome”) as an independent technical expert in this proceeding before the United States Patent and Trademark Office (“PTO”) Patent Trial and Appeal Board (“Board”) regarding U.S. Patent No. 11,560,354 (“the ’354 patent”).

2. I understand that Hikma Pharmaceuticals USA Inc., (“Hikma” or “Petitioner”) filed a petition for *Inter Partes* Review of the ’354 patent, which includes the Declaration of Dr. Salvatore Lepore (“Lepore Declaration”).

3. I have been asked by counsel for Axsome to analyze and respond to opinions set forth in the Lepore Declaration.

4. I am being compensated for my time spent in connection with this matter at a rate of \$750 per hour. My compensation does not depend on the outcome of the proceeding or the conclusions in my declaration. I have no other interest in this proceeding.

II. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

1. My qualifications and professional experience, including a list of my publications and my expertise and professional activities, are described in my

curriculum vitae, a copy of which is provided with this Declaration as Exhibit 2016.

The following is a summary of my qualifications and professional experience.

5. I am an independent consultant and the president of Chyall Pharmaceutical Consulting, LLC (“Chyall Pharma”), which is my pharmaceutical consulting business. I am a Ph.D. chemist with expertise in the study of organic materials and the synthesis, characterization, and analytical testing of pharmaceutical drug substances and drug products.

6. I obtained my Bachelor of Arts degree with a major in chemistry from Oberlin College in 1986, and my Ph.D. in chemistry from the University of Minnesota in 1991. My doctoral research concerned the synthesis and characterization of novel organic molecules, and my dissertation focused on synthesizing and understanding the reactivity of high-energy cyclopropane molecules. I was a postdoctoral fellow from 1992 to 1996 in the chemistry department at Purdue University, where I studied the properties and reactivity of organic molecules using the techniques of mass spectrometry. My research involved both small molecular weight molecules as well as large biological molecules.

7. Following my postdoctoral fellowship, I worked as a research chemist at Great Lakes Chemical Corporation (“Great Lakes Chemical”), which is now part of LANXESS. Great Lakes Chemical was a specialty chemicals company that

manufactured and sold organic compounds that are used in a diverse range of commercial products. During my employment at Great Lakes Chemical, the company manufactured chemicals that were sold as polymer additives, fire suppression agents, biocides, fuel additives, pesticides, water treatment chemicals, food additives, and pharmaceutical intermediates and products, among other applications.

8. I worked in the corporate research and development department at Great Lakes Chemical, with the mandate of identifying new technologies and products to sell into existing and emerging specialty chemicals markets. I gained experience in the development of multi-step chemical processes and products that were taken from the laboratory to commercial production. Several of Great Lakes Chemical's products were manufactured at scales exceeding several million pounds of material per year. As a research chemist at Great Lakes Chemical, I worked on chemical processes that involved highly reactive and corrosive chemicals such as bromine, chlorine, fuming sulfuric acid, and phosphoryl trichloride, among other hazardous chemicals. I have practical experience with chemical processes that are conducted on laboratory, pilot plant, and full commercial scales.

9. In 2000, I joined SSCI, Inc. (subsequently acquired by and renamed Aptuit, Inc.) as a Research Investigator. In 2003, I was promoted to Senior

Research Investigator. In 2007, I was promoted to Principal, and in 2010, I was promoted to Director. While at SSCI/Aptuit, I served as project leader and group manager for external client projects involving various aspects of organic and analytical chemistry. I was also involved in the development of new pharmaceutical products and providing outside testing for chemical products.

10. I remained with SSCI/Aptuit until 2011, when I founded my own scientific consultancy, Chyall Pharma. Through Chyall Pharma, I consult on topics pertaining to the chemistry of pharmaceutical drug substances, including crystal polymorphism, salt and cocrystal technologies, amorphous materials, enantiomer resolution and solid form stability technologies. I continue to operate Chyall Pharma today.

11. In November 2022, I joined Improved Pharma, a consortium of scientists providing contract research and consulting services to the pharmaceutical industry. Improved Pharma maintains a research laboratory located in the Purdue University Research Park. Since joining Improved Pharma, I have worked on projects concerning the solubility, nucleation, and crystallization of organic compounds under various conditions including hypergravity and microgravity, and the formation and identification of polymorphs, salts, and cocrystals for compounds with potential pharmaceutical applications.

12. I have authored or co-authored 23 publications in peer-reviewed scientific journals that are listed in my *curriculum vitae* attached as Exhibit 2016. My most recent publications involve research topics in the pharmaceutical sciences. I am a co-inventor on five patents granted by the PTO. I have given numerous scientific presentations at various technical meetings that are described in my *curriculum vitae*.

13. Through my education and work experiences, I have obtained extensive education and training in chemistry with specific experience in the areas of organic chemistry and pharmaceutical sciences. I have worked on numerous projects providing research and consulting services related to the development of pharmaceutical drug substances and pharmaceutical products. At SSCI, I managed protocol studies conducted for clients who sought to identify suitable solid forms of their drug candidates. Some of this work involved attempting to produce different salt forms of a drug candidate and conducting further characterization (e.g., stability studies, assays for purity, crystal form screening experiments) in order to identify forms of the drug candidate for further development. Through my education and work experience, I have conducted characterization (e.g., structural elucidation, dissolution, solubility, and stability studies) of various compounds to identify appropriate solid forms for further development.

14. I have directed research projects conducted on behalf of clients who were interested in quantitative determinations of the purity and contents of various products (e.g., assay determinations). Other projects involved determining the identity and quantity of levels of impurities in products and mixtures. I have conducted stability studies on pharmaceutical products to assay the purity and/or determine impurity profiles of those products under various conditions. I have also worked on research projects concerning the development of analytical methods for the characterization and stability of compounds used in pharmaceutical applications.

15. Over the course of my 30-year career as a chemist, I have gained significant expertise in numerous technologies and instrumental techniques that are used to characterize organic compounds. These techniques include methods for crystallization of solid compounds, chromatography techniques (e.g., liquid and gas column chromatography, TLC and HPLC), mass spectrometry (MS), X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Infrared (IR) and Raman spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, particle size analysis, optical microscopy, mass spectrometry, and dynamic vapor sorption analysis, among others.

16. I have worked on projects involving the characterization of drug substances that have been formulated into final dosage forms. I have investigated the reactivity of pharmaceutical drug substances and excipients as a function of the processes used to manufacture the corresponding drug products. I have worked on the development of pharmaceutical products for oral, parenteral, topical, and transdermal administration. I understand and am familiar with various technologies used to synthesize drug substances and manufacture drug products.

III. MATERIALS CONSIDERED

17. The opinions contained in this Declaration are based on the documents I reviewed, as well as my education, years of professional experience, and knowledge. In forming my opinions expressed in this Declaration, I reviewed the following documents and other materials cited herein in this Declaration: the Lepore Declaration and all materials cited therein, the Petition for *Inter Partes* Review of U.S. Patent No. 11,560,354, and Exs. 2002, 2003, 2005-11, 2014-2021.

18. This Declaration presents the opinions I have formed at the present time. I reserve the right to revise, supplement, or amend my opinions as well as the bases for my opinions stated in this Declaration based on any new information that I may be asked to review.

IV. SUMMARY OF OPINIONS

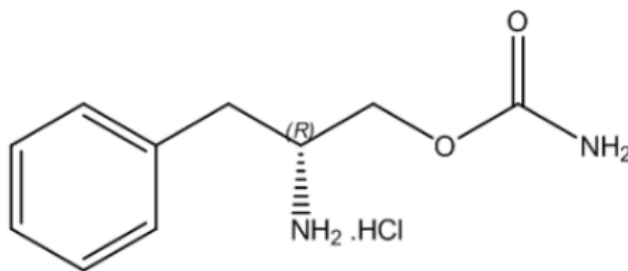
19. In my opinion, none of the references Dr. Lepore relies on in his declaration disclose, teach, or suggest that 2-chloropropane would be an impurity present with solriamfetol hydrochloride. *See infra* at VI, VII. In particular, as I explain in detail below, Choi268 discloses a preparation of solriamfetol hydrochloride that does not mention or suggest the presence of 2-chloropropane, and Kaleemullah likewise does not disclose, teach, or suggest the presence of 2-chloropropane in solriamfetol hydrochloride. *See infra* at VII.A. In my opinion, Kaleemullah does not mention solriamfetol hydrochloride, and moreover, discloses that its analytical technique did NOT detect residual alkyl chloride (including 2-chloropropane) in the tested drug substance samples. *See infra* at VI.B. As I explain below, the presence of 2-chloropropane in solriamfetol hydrochloride cannot be inferred from the analysis disclosed in Kaleemullah. *See infra* at VII.B. In view of the lack of disclosure, there would be no motivation to modify the art to arrive at the claimed compositions of the '354 patent. In addition, due to the unpredictability in the art, there would be no reasonable expectation that a POSA could modify the art to arrive at the claimed compositions without extensive experimentation. *See infra* at VIII.

v. OVERVIEW OF THE '354 PATENT

20. Dr. Lepore states that, “[f]or the purposes of this Declaration, I am applying September 6, 2016, as the priority date of the 354 Patent.” Lepore Declaration at ¶ 31. I do the same in my analysis.

21. Dr. Lepore proposes that a person of ordinary skill in the art or (“POSA” or “POSITA”) “in September 2016 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, a POSITA would have had a 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.” Lepore Declaration at ¶ 28. I have been asked by counsel to accept and apply this definition of a POSA for purposes of this declaration, which I have throughout my analysis. I am, and was in September 2016, a person of at least ordinary skill under Dr. Lepore’s proposal.

22. The ’354 patent discloses compositions that include (R)-2-amino-3-phenylpropyl carbamate hydrochloride (“solriamfetol hydrochloride” or “solriamfetol HCl”) and 2-chloropropane. The structure of solriamfetol hydrochloride is:



Ex. 2002 at 12.

23. The claims of the '354 patent relate to compositions that comprise solriamfetol hydrochloride and 2-chloropropane. Counsel has asked me to assume for purposes of my declaration that the claims require a non-zero amount of 2-chloropropane. This request, in my opinion, is consistent with how a POSA would understand the claims given that they are directed to compositions that must comprise solriamfetol hydrochloride and 2-chloropropane. Independent claim 1 is reproduced below, with the relevant language highlighted.

What is claimed is:

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

Ex. 1001 at Claim 1.

VI. RESPONSE TO DR. LEPORE'S GROUND 1 REFERENCES

24. Dr. Lepore relies on three references for his Ground 1 opinion. They are U.S. Patent Application Publication No. 2005/0080268 (Ex. 1006, "Choi268"); *Development and Validation of Gas Chromatography Method for Low Level Detection of Residual Methyl Chloride, Ethyl Chloride and Isopropyl Chloride in*

Ziprasidone Hydrochloride (Ex.1016, “Kaleemullah”); and U.S. Application Publication No. 2009/0312416 (Ex.1005, “Ahnaou”). Lepore Declaration at ¶¶ 48-59. Dr. Lepore refers to these three references as “The Principal Prior Art.” Lepore Declaration at ¶ 48. I address these references immediately below. I also address an additional reference that Dr. Lepore relies on: *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) (Ex. 1007, “Kim”). In particular, counsel has asked me to address whether the information that Dr. Lepore relies on from Kaleemullah is substantially the same as the information that Dr. Lepore relies on from Kim.

A. Choi268

25. I have reviewed Dr. Lepore’s summary of Choi268. Relevant to responding to Dr. Lepore’s opinions here, I note that Example 1 of Choi268 provides a procedure for the synthesis of solriamfetol hydrochloride. Ex. 1006 at [0068]-[0069]. Choi268 as a whole, including the synthetic procedure set forth in Example 1, does not mention or provide any information regarding 2-chloropropane. *Id.*; see generally Ex. 1006. In my opinion, a POSA reviewing Choi268 would not understand it to teach or suggest that the resulting product of the synthesis would comprise solriamfetol hydrochloride and 2-chloropropane. In fact, based on my review of Dr. Lepore’s declaration and the references cited

therein, I see no teaching or suggestion of solriamfetol hydrochloride with any 2-chloropropane impurity in any prior art.

B. Kaleemullah

26. I have reviewed Dr. Lepore’s summary of Kaleemullah. Relevant to responding to Dr. Lepore’s opinions here, I note that Kaleemullah is a journal article that teaches a headspace gas chromatography (“GC”) technique developed to analyze potentially low levels of impurities in five different drug substances. Ex. 1016 at Abstract; *see generally* Ex. 1016. Kaleemullah’s main focus is on the development and validation of a headspace GC analytical technique to detect and assay potential 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”). It then discusses the potential application of the GC technique to four other drug substances – risperidone, alfuzosin HCl, valganciclovir HCl, and fluoxetine HCl. Ex. 1016 at 8. This article does not mention solriamfetol hydrochloride at all. Kaleemullah does not identify or suggest a predetermined expectation in finding impurities in the drug substances tested, nor does the article draw any conclusions about the probability or likelihood of finding impurities. Kaleemullah reports that its method is capable of finding impurities if they are present, but it does not suggest that the analytical technique determines the

probability that those impurities are present in the preparations of the drugs substances, *i.e.*, the active pharmaceutical ingredients (“API”).

27. Per the method validation, the determination of impurities by the analytical techniques in Kaleemullah would be considered to be routine work by a POSA, yet knowing which impurities (including 2-chloropropane) may or may not be present is unpredictable. The analysis in Kaleemullah, compared to Dr. Lepore’s assumption that 2-chloropropane will result in a reaction when both hydrochloric acid and isopropyl alcohol are used (*see, e.g.*, Lepore Declaration at ¶ 85), confirm this unpredictability. Kaleemullah specifically reports that “[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 particular, the results in Kaleemullah demonstrate that 2-chloropropane is not formed in the synthesis of ziprasidone hydrochloride. As such, having an analytical method for measuring an impurity does not suggest the necessary presence of that impurity or any reasonable likelihood that the potential impurity will be present in an API.

28. Indeed, for all of the five drug substances that were analyzed in Kaleemullah, there was no disclosure that taught or suggested whether impurities would be present or absent in a particular sample, unless impurities were

intentionally added to a sample. Four of the five tested drug substances, including the ziprasidone hydrochloride, were hydrochloride salts. According to Kaleemullah, “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.” Ex. 1016 at 8. Kaleemullah states 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.* This is confirmed by the data in Table 4, which show the presence of alkyl chloride residue at or near the amount spiked into the sample. *Id.*

C. Ahnaou

29. I have reviewed Dr. Lepore’s summary of Ahnaou. Relevant to responding to Dr. Lepore’s opinions here, I note that Ahnaou does not mention or provide any information regarding 2-chloropropane. *See generally* Ex. 1005. In my opinion, a POSA reviewing Ahnaou would not understand it to teach or suggest a composition comprising solriamfetol hydrochloride and 2-chloropropane. In fact, based on my review of Dr. Lepore’s declaration and the references cited therein, I see no teaching or suggestion of solriamfetol hydrochloride with any 2-chloropropane impurity in any prior art.

D. Kim

30. Again, I have been asked by counsel to address whether the information that Dr. Lepore relies on from Kaleemullah is substantially the same as the information available in Kim. In my opinion, a POSA would understand the information to be substantially the same between the two references.

31. Throughout his declaration, Dr. Lepore relies on Kaleemullah for, what Dr. Lepore opines, is the genotoxic impurity 2-chloropropane resulting from reaction with hydrochloric acid and isopropyl alcohol. *See, e.g.*, Lepore Declaration at ¶ 62. Dr. Lepore further relies on Kaleemullah for, what Dr. Lepore opines, is a disclosure to reduce genotoxic impurities. *Id.* at ¶ 89. I have already addressed my disagreement with Dr. Lepore's views above. *See supra* at VI.B. Regardless, this is the same as the opinions Dr. Lepore offers with respect to Kim. *See id.* at ¶ 97.

VII. FURTHER RESPONSES TO DR. LEPORE'S OPINIONS

A. Choi268 and Kaleemullah do not teach or suggest the presence of 2-chloropropane in solriamfetol hydrochloride

32. Dr. Lepore cites Choi268 alone for the disclosure of a procedure for the organic synthesis of solriamfetol hydrochloride, but he admits that "Choi268 does not expressly disclose the formation of '2-chloropropane.'" Lepore Declaration at ¶ 60. In my opinion, a POSA would understand that Choi268 does not mention or otherwise provide any hint at the presence of 2-chloropropane in

solriamfetol hydrochloride. In fact, 2-chloropropane is not mentioned in Choi268 at all. *See generally* Ex. 1006. And Dr. Lepore does not provide any evidence in the prior art, or any reproduction of Choi268's Example 1 procedure, to support any opinion that Choi268's procedure results in a product that contains 2-chloropropane. In my opinion, without actual data showing that Choi268's procedure results in a product containing 2-chloropropane, or any suggestion or mention of 2-chloropropane as an impurity, a POSA would not have known that 2-chloropropane was an issue to be solved, let alone have been motivated to modify the procedure disclosed in Choi268 to reduce amounts of 2-chloropropane.

33. Given his concession regarding Choi268's lack of disclosure, Dr. Lepore opines that 2-chloropropane "would be formed" in Choi268's procedure in view of the disclosure in Kaleemullah. Lepore Declaration at ¶ 60. But in my opinion, a POSA would not understand either of Choi268 or Kaleemullah to teach or suggest the presence of 2-chloropropane in solriamfetol hydrochloride or its formation during the synthesis of solriamfetol hydrochloride. To begin, Kaleemullah does not mention solriamfetol hydrochloride at all. In my opinion, and consistent with Kaleemullah's disclosures, the use of an analytical method of detection for 2-chloropropane does not suggest the existence of 2-chloropropane in tested reaction products, much less for a product that is not analyzed in Kaleemullah – solriamfetol hydrochloride.

34. Dr. Lepore opines that Kaleemullah suggests that for a different drug substance – ziprasidone hydrochloride – “treating ziprasidone base ‘in alcohol solvent (Methanol, Ethanol, or Isopropanol) . . . with hydrochloric acid’ results in the formation of ‘[i]sopropyl chloride’” is an “express disclosure of the formation of ‘2-chloropropane’ during salt precipitation with HCl and isopropanol.” Lepore Declaration at ¶ 60 (emphasis added). This is incorrect. As I summarized above, Kaleemullah does not disclose the formation of 2-chloropropane in ziprasidone hydrochloride, nor does the assay technique validated in Kaleemullah detect the presence of 2-chloropropane in any of the five drug substances that were analyzed unless the 2-chloropropane was specifically spiked into the sample for testing purposes. *See supra* at VI.B. The only teaching Kaleemullah imparts to a POSA, in my opinion, is that for the preparation of all of its disclosed drug substances that may include a precipitation step using hydrochloric acid and alcohol (e.g., isopropanol, ethanol, methanol), none of the products result in detectable amounts of an alkyl chloride impurity.

B. The presence of 2-chloropropane cannot be inferred from the synthesis or analysis of different APIs

35. Beyond the lack of disclosures supporting Dr. Lepore’s opinions that I note above, it is further my opinion that a POSA would not have been motivated to modify the disclosed synthesis of solriamfetol hydrochloride in Choi268 with the teachings of Kaleemullah. In my opinion, the mere existence of a headspace GC

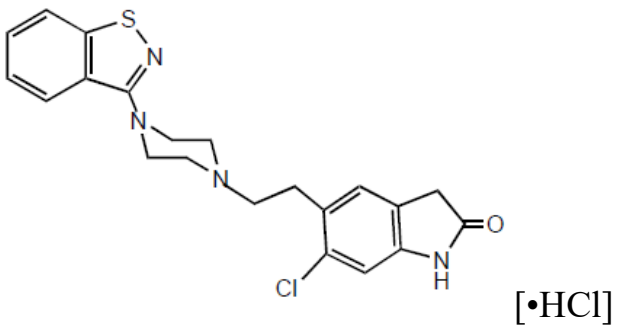
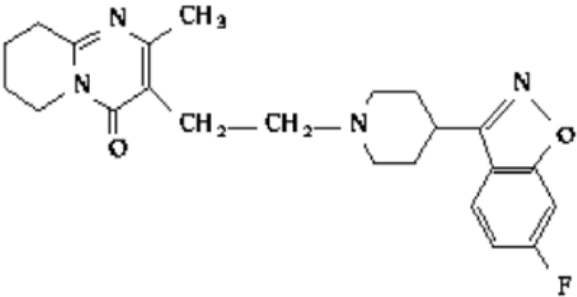
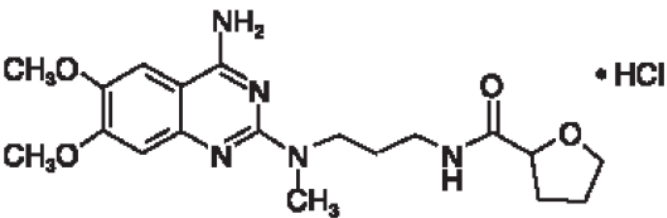
method to detect potential volatile alkyl chloride impurities in different APIs would not teach a POSA anything about the existence of any specific impurity in an unrelated compound. A POSA understands that the ability to detect impurities by analytical techniques (including GC) is routine, but that the experimentation to determine specific reaction conditions and reagents that will contribute to impurities (including 2-chloropropane) in an API is something that cannot be predicted and is definitely not routine.

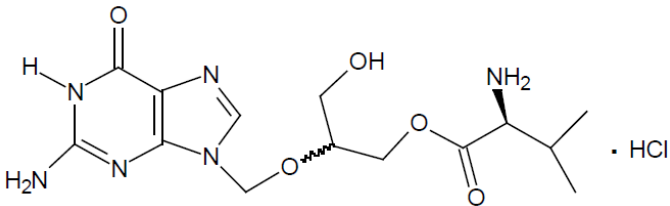
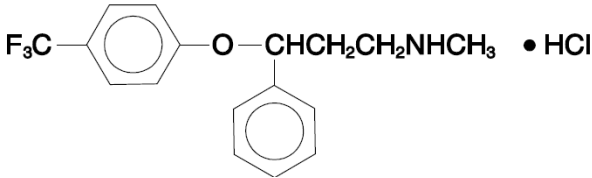
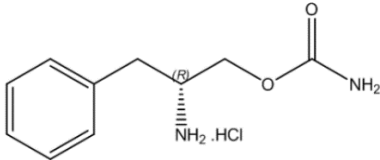
36. Many pharmaceutical products are formulated with the API along with other ingredients that serve vital roles in the manufacture, safety, and efficacy of the product but do not have a therapeutic effect. These other ingredients are known as excipients or inactive ingredients.

37. The API is generally prepared in multi-step chemical syntheses. Kaleemullah does not disclose the processes used in the organic synthesis of the five drug substances being analyzed. Kaleemullah also does not teach or suggest that the organic synthesis of the five different substances would be the same. The prior art shows that the five drug substances were synthesized by many different procedures, resulting in different levels of purity and different assay results (if reported). See 2011 at Example 16; Ex. 2017 at Examples 1-3; Ex. 2018 at Examples 4, 6, 8; Ex. 2019 at Examples 1-4; Ex. 2020 at Examples 1-5; Ex. 2021 at Example 1(d). Because the structures of each are so different from each other as

can be seen from Table 1 below, a POSA would surmise that the organic synthesis of one would not be the same as another. I have included the structure of solriamfetol hydrochloride as well; its structure is also very different from the five APIs analyzed in Kaleemullah. In short, a POSA would understand that there is nothing in Kaleemullah that suggests that the presence of impurities from the synthesis of solriamfetol hydrochloride could be inferred from the GC technique or the analysis of the five drug substances in Kaleemullah.

Table 1: Chemical Structures of APIs

Ziprasidone HCl (See Ex. 2005 at 16) Note: Structure as shown in the reference is of the freebase. I have added the HCl to show the salt form.	
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)	

38. Additionally, it is my opinion that a POSA would not be motivated to modify a solriamfetol hydrochloride procedure based on the synthesis of a compound that is drastically different structurally, has different properties, contains different impurities, and was made pursuant to an unrelated process, because a POSA knows that the synthesis of organic compound is unpredictable. In my opinion, a POSA would not look to Kaleemullah's disclosure of ziprasidone hydrochloride, or any of the other APIs, to understand, motivate, or predict anything about the organic synthesis of solriamfetol hydrochloride.

39. In my opinion, a POSA reviewing Kaleemullah would not understand it to teach or suggest anything regarding the resulting product from a solriamfetol hydrochloride synthesis, let alone if it would comprise 2-chloropropane.

C. If alkyl chloride impurities were a known issue in Choi268, then a POSA would have eliminated synthetic steps

40. Based on my discussion of the lack of support for Dr. Lepore's opinion that 2-chloropropane would be an impurity resulting from the procedure disclosed in Example 1 of Choi268 as well as Kaleemullah teaching away from the formation of alkyl chloride in APIs (*see supra* at VII.A), it is my opinion that a POSA would not have been motivated to look to any techniques/references to attempt to minimize the level of an 2-chloropropane in solriamfetol hydrochloride.

41. It is my opinion that a POSA would not know, or have reason to believe, that 2-chloropropane was present as an impurity in the solriamfetol hydrochloride prepared according to Choi268. But, for argument's sake, even if I accept the premise that the presence of 2-chloropropane was known in the product that results from Choi268 Example 1 (due to a reaction between isopropanol and HCl), given that Dr. Lepore also maintains that it was genotoxic (*see, e.g.*, Lepore Declaration at ¶ 62), then it is my opinion that a POSA would have been motivated to change or omit synthetic steps that cause the formation of the 2-chloropropane in Dr. Lepore's view. The simplest change that could have been made would be to swap the isopropanol used in the procedure for another solvent, as the solvent is simply the medium for the acid-base reaction and isolation of the solid product. For example, one could have used THF rather than isopropanol. *See e.g.*, Ex. 2010 at 4:43-5:37 (disclosing solriamfetol salt precipitation in several non-alcohol

solvents including THF and ethyl acetate); *see also e.g.*, Ex. 2011 at Example 16 (disclosing the use of diethyl ether in the synthesis of ziprasidone hydrochloride). If Dr. Lepore's opinions regarding the formation of 2-chloropropane are accepted, then this solvent swap would eliminate the formation of 2-chloropropane by removing the key reactant that Dr. Lepore opines results in the formation of 2-chloropropane. In my opinion, the fact that the Dr. Lepore does not consider this simple change to Choi268 Example 1, or any other changes that a POSA might be motivated to make, shows that the Dr. Lepore's arguments are hindsight driven. In my opinion, under a situation where Dr. Lepore's opinions regarding the formation of 2-chloropropane are accepted and there is concern that 2-chloropropane is a genotoxic impurity, then a POSA would have been motivated to completely eliminate the formation of 2-chloropropane from the synthetic process of Choi268 Example 1 rather than keeping isopropanol as the solvent medium for salt precipitation.

VIII. A POSA would not have any expectations, let alone a reasonable expectation, in arriving at the claimed compositions

42. Dr. Lepore alleges that a POSA would have a reasonable expectation of success in arriving at the claimed compositions of solriamfetol hydrochloride and 2-chloropropane based on what he calls "routine experimentation." *See, e.g.*, Lepore Declaration at ¶ 68. He relies on two references for this position:

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) (Ex. 1019, “Yang”); and Kim. By responding to Kaleemullah, I respond to Kim given their overlapping nature. I further address Yang below, and also further comment on Kim.

43. Dr. Lepore repeats Yang’s disclosure “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.” Lepore Declaration at ¶ 94. However, in my opinion, a POSA would understand that Dr. Lepore’s reliance on Yang is misplaced as the “solution[]” used in Choi268 is not “methanolic” but rather is isopropanol. See Ex. 1006 at [0068]-[0069]. Dr. Lepore does not provide any explanation as to why a reaction parameter in methanol solutions would be identical to those in isopropanol solutions, let alone that any of these conditions are routine—which they are not. Further, there is no explanation how any of the reaction parameters (e.g., Yang and Kim’s parameter variables including solvent type, temperature, acid concentration, acid exposure time, and charging of water) have anything to do with the reaction of solriamfetol hydrochloride—let alone provide a POSA with any expectations regarding a solriamfetol hydrochloride synthesis.

44. Furthermore, nothing about modifying Choi268 Example 1 is simply “routine experimentation” as Dr. Lepore claims. In fact, Dr. Lepore does not mention, let alone comment upon the multiple variables that are present in the synthetic procedure of Example 1 that a POSA would need to consider. Example 1 of Choi268 discloses a basic procedure to synthesize solriamfetol hydrochloride that contains many variables, any one of which could alter the composition of the resulting product. *See* Ex. 1006 at [0068]-[0069]. In addition to the five process variables discussed above, Choi268 Example 1 also contains several additional variables that could alter the final product which include: 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 the 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]. As such, a POSA would not have any expectation of what comprises the product of Choi268 Example 1, including the presence of impurities, let alone know that 2-chloropropane was present. In my opinion, nothing about Dr. Lepore’s proposed modification of reaction conditions to Choi268 Example 1 are routine on their own, and when combined with the process variables of Choi268 Example 1, they make any expectations regarding a reaction of solriamfetol hydrochloride anything but predictable. In short, a POSA would have no reasonable expectation of levels of 2-chloropropane present in the product, if any, when the procedure was modified.

45. It is well known that the synthesis of an organic compound, moving from starting materials to a final product, involves a multitude of variables and is thus, extremely complex. Variables that exist in the synthetic scheme for any given compound include, but are not limited to: temperature, pressure, time, rate, kinetics, solvents, atmosphere, concentration, technique, analytical analysis,

equipment, reagent grade, quality of starting material(s)—any one of which can drastically impact the composition and overall properties of the final synthetic product. Ex. 2015 at 4 (disclosing that impurities in starting materials can impact resulting product, “Note that the impurities may carry forward in the downstream chemistry and/or may react to form new synthetic by-products”), *id.* at 5 (“Impurities in the drug substance can originate from incomplete reactions, over-reactions, and side reactions and can also originate from impurities in starting materials, reaction solvents, catalysts, or residual solvents”).

A. The '354 patent documented failures leading up to the invention further support my opinions regarding the lack of any reasonable expectation of success

46. In my opinion, the '354 patent itself is illustrative of the unpredictability in organic synthesis, specifically in making solriamfetol hydrochloride. The '354 patent discusses repeated failed efforts to obtain a solriamfetol hydrochloride product with low levels of 2-chloropropane. See Ex. 1001 at 10:53-11:27. Specifically, steps that could potentially remove 2-chloropropane, such as “[d]rying the crystals, even at elevated temperatures” and “[r]eslurrying the crystals” were “ineffective” at reducing the amount of 2-chloropropane to the claimed levels. *Id.* at 11:13-15. Also, attempts to alter the crystallization conditions to avoid the formation of 2-chloropropane by swapping isopropanol with isopropyl acetate were made; however, “the crystallization was

poorly controlled, resulting in the formation of a thick crust in the reactor, and produced very small crystals.” *Id.* at 11:18-22. Further attempts made included “[c]harging the HCl gas at a lower temperature (30-35 degrees C.)” which “controlled [the] formation of 2-CP;” however, once again, “the crystallization was poorly controlled, resulting in the formation of a thick crust in the reactor, and produced a less crystalline material.” *Id.* at 11:22-27. Moreover, it was discovered that “charging of HCl in gas form cause unwanted spontaneous crystallization in the conditions evaluated,” so next attempts included “adding HCl in the form of a 37% aqueous solution,” “increas[ing] the total amount of water 1.76-fold . . . so the resulting suspension [could] be cooled to a lower temperature to maximize the yield,” but “the larger amount of water combined with the lower molar excess of acid . . . and the lower temperature contributes to minimizing the rate of formation of 2-CP.” *Id.* at 11:28-37.

47. Ultimately, the inventors needed to change multiple variables from the initial preparation to obtain an acceptable product 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 a saturated solution of the gas), 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 a dry nitrogen stream (rather than drying at room temperature at reduced pressure).

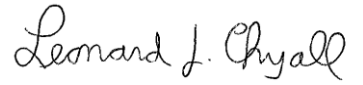
48. None of the above failures or successes for solriamfetol hydrochloride with low levels of 2-chloropropane are present in the art provided by Dr. Lepore, nor does Dr. Lepore opine that they were. Therefore, it is my opinion that there was no guidance or direction in the prior art that would have led to any expectation, let alone a reasonable expectation, in arriving at the claimed composition. In my opinion, failures that resulted from different variable modifications and the ultimate solution that involved making changes to multiple process variables show that the claims of the '354 patent are anything but the result of "routine experimentation." Furthermore, it is my opinion that the fact that Dr. Lepore fails to provide substantive explanations regarding any of these process variables as applied to Choi268 Example 1 and ignores the process modification failures disclosed in the '354 patent, shows that the Dr. Lepore's opinions are rooted in hindsight.

IX. DECLARATION STATEMENT

49. I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true,

and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Executed on January 23, 2025

A handwritten signature in cursive script, reading "Leonard J. Chyall", positioned above a horizontal line.

Lenard J. Chyall, Ph.D.