

Paper No. ____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SUN PHARMACEUTICAL INDUSTRIES, INC.,
Petitioner

v.

NIVAGEN PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2025-_____

U.S. Patent No. 11,878,076

Declaration of Raj Suryanarayanan, Ph.D.

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. QUALIFICATIONS.....	1
III. MATERIALS CONSIDERED.....	4
IV. LEVEL OF ORDINARY SKILL IN THE ART	6
V. RELEVANT LEGAL STANDARDS	7
VI. OVERVIEW OF THE '076 PATENT.....	8
A. Summary of the '076 Patent and the Challenged Claims.....	9
B. Prosecution History of the '076 Patent.....	19
VII. BACKGROUND ON THE TECHNOLOGY OF THE '076 PATENT AND THE STATE OF THE ART	22
A. Phenobarbital Sodium and Its Harmful Degradants.....	23
B. Active Pharmaceutical Ingredients and Pharmaceutical Compositions and Strategies for Impurity Control	25
C. Lyophilization of Pharmaceutical Products.....	30
D. Storage Conditions and Stability Testing	33
VIII. CLAIM CONSTRUCTION	37
IX. INVALIDITY GROUND 1: THE CHALLENGED CLAIMS ARE OBVIOUS OVER PIF, IN VIEW OF PARKER AND WEST-WARD	38
A. Overview of the PIF.....	41
B. Overview of Parker.....	43
C. Overview of West-Ward	44
D. Motivation to Combine Ground 1 References with a Reasonable Expectation of Success	44
E. Obviousness of Claim 1 — Element by Element Claim Analysis	50
F. Obviousness of Claim 2 — Element by Element Claim Analysis	58
G. Obviousness of Claim 3 — Element by Element Claim Analysis	61
H. Obviousness of Claim 4 — Element by Element Claim Analysis	62

I. Obviousness of Claim 5 — Element by Element Claim Analysis	63
J. Obviousness of Claim 6 — Element by Element Claim Analysis	64
K. Obviousness of Claim 7 — Element by Element Claim Analysis	66
L. Obviousness of Claim 8 — Element by Element Claim Analysis	67
M. Obviousness of Claim 9 — Element by Element Claim Analysis	68
N. Obviousness of Claim 10 — Element by Element Claim Analysis	68
O. Obviousness of Claim 11 — Element by Element Claim Analysis	69
P. Obviousness of Claim 12 — Element by Element Claim Analysis	69
Q. Obviousness of Claim 13 — Element by Element Claim Analysis	70
R. Obviousness of Claim 14 — Element by Element Claim Analysis	70
S. Obviousness of Claim 15 — Element by Element Claim Analysis	72
T. Obviousness of Claim 16 — Element by Element Claim Analysis	72
U. Obviousness of Claim 17 — Element by Element Claim Analysis	74
V. Obviousness of Claim 18 — Element by Element Claim Analysis	74
W. Obviousness of Claim 19 — Element by Element Claim Analysis.....	74
X. Obviousness of Claim 20 — Element by Element Claim Analysis	75
X. INVALIDITY GROUND 2: THE CHALLENGED CLAIMS ARE ANTICIPATED BY THE '608 PUBLICATION	76
A. The '076 Patent is Not Entitled to a Priority Date Earlier Than June 30, 2022 76	
B. Overview of the '608 Publication.....	88
C. Anticipation of Claim 1 — Element by Element Claim Analysis.....	101
D. Anticipation of Claim 2 — Element by Element Claim Analysis.....	103
E. Anticipation of Claim 3 — Element by Element Claim Analysis.....	104
F. Anticipation of Claim 4 — Element by Element Claim Analysis.....	105
G. Anticipation of Claim 5 — Element by Element Claim Analysis.....	106
H. Anticipation of Claim 6 — Element by Element Claim Analysis.....	107
I. Anticipation of Claim 7 — Element by Element Claim Analysis.....	110

J. Anticipation of Claim 8 — Element by Element Claim Analysis.....	112
K. Anticipation of Claim 9 — Element by Element Claim Analysis.....	113
L. Anticipation of Claim 10 — Element by Element Claim Analysis.....	113
M. Anticipation of Claim 11 — Element by Element Claim Analysis	114
N. Anticipation of Claim 12 — Element by Element Claim Analysis.....	114
O. Anticipation of Claim 13 — Element by Element Claim Analysis.....	115
P. Anticipation of Claim 14 — Element by Element Claim Analysis.....	115
Q. Anticipation of Claim 15 — Element by Element Claim Analysis.....	117
R. Anticipation of Claim 16 — Element by Element Claim Analysis.....	117
S. Anticipation of Claim 17 — Element by Element Claim Analysis.....	118
T. Anticipation of Claim 18 — Element by Element Claim Analysis.....	118
U. Anticipation of Claim 19 — Element by Element Claim Analysis.....	119
V. Anticipation of Claim 20 — Element by Element Claim Analysis.....	119
XI. INVALIDITY GROUND 3: THE CHALLENGED CLAIMS ARE OBVIOUS OVER THE '608 PUBLICATION AND THE ORDINARY KNOWLEDGE OF A POSA	120
A. Motivation to Make Lyophilized Phenobarbital Sodium Pharmaceutical Products Covered by the Challenged Claims with a Reasonable Expectation of Success.....	121
B. Obviousness of Claim 1 — Element by Element Claim Analysis	126
C. Obviousness of Claim 2 — Element by Element Claim Analysis	129
D. Obviousness of Claim 3 — Element by Element Claim Analysis	131
E. Obviousness of Claim 4 — Element by Element Claim Analysis	132
F. Obviousness of Claim 5 — Element by Element Claim Analysis	134
G. Obviousness of Claim 6 — Element by Element Claim Analysis	134
H. Obviousness of Claim 7 — Element by Element Claim Analysis	137
I. Obviousness of Claim 8 — Element by Element Claim Analysis	139
J. Obviousness of Claim 9 — Element by Element Claim Analysis	140

K. Obviousness of Claim 10 — Element by Element Claim Analysis	140
L. Obviousness of Claim 11 — Element by Element Claim Analysis	141
M. Obviousness of Claim 12 — Element by Element Claim Analysis	141
N. Obviousness of Claim 13 — Element by Element Claim Analysis	142
O. Obviousness of Claim 14 — Element by Element Claim Analysis	142
P. Obviousness of Claim 15 — Element by Element Claim Analysis	145
Q. Obviousness of Claim 16 — Element by Element Claim Analysis	145
R. Obviousness of Claim 17 — Element by Element Claim Analysis	146
S. Obviousness of Claim 18 — Element by Element Claim Analysis	146
T. Obviousness of Claim 19 — Element by Element Claim Analysis	147
U. Obviousness of Claim 20 — Element by Element Claim Analysis	147
XII. OBVIOUSNESS – SECONDARY CONSIDERATIONS	148
XIII. THE PETITION SHOULD NOT BE DISCRETIONARILY DENIED	151
A. Part 1: The Same or Substantially the Same Art and Arguments Were Not Previously Presented to the Patent Office	153
1. Factor (a): The Similarities and Material Differences Between the Asserted Art and the Prior Art Involved During Examination	153
2. Factor (b): The Cumulative Nature of the Lead Asserted Art and the Prior Art Evaluated During Examination.....	155
3. Factor (d): The Extent of the Overlap Between the Arguments Made During Examination and the Manner in Which Petitioner Relies on the Prior Art or Patent Owners Distinguish the Prior Art.....	156
XIV. AVAILABILITY FOR CROSS EXAMINATION	158

I, Raj Suryanarayanan, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. I have been retained as an expert by counsel for Sun Pharmaceutical Industries, Inc. (“Petitioner”). I have been asked by counsel to provide my expert opinions regarding the validity of claims 1-20 of U.S. Patent No. 11,878,076 (the “’076 Patent”), assigned to Nivagen Pharmaceuticals, Inc. (“Patent Owner”), in support of Petitioner’s Petition for Inter Partes Review (“Petition”) of the ’076 Patent. For the reasons set forth below, it is my opinion that claims 1-20 (the “challenged claims”) are unpatentable.

II. QUALIFICATIONS

2. I am currently a Professor and the William & Mildred Peters Endowed Chair in the Department of Pharmaceutics at the University of Minnesota, College of Pharmacy.

3. I obtained my Bachelor of Pharmacy (B.Pharm.) degree from the Indian Institute of Technology, Varanasi, India in 1976. In 1978, I earned my Master of Pharmacy (M.Pharm.) degree from Banaras Hindu University, Varanasi, India. I further obtained my Master of Science (M.Sc.) in Pharmaceutics and my Ph.D. in Pharmaceutics from the University of British Columbia, Vancouver, Canada in 1981 and 1985, respectively. From 1989 to 1990, I was a visiting research scholar at the Laboratory of Dr. Peter York in the Department of

Pharmaceutical Technology at the School of Pharmacy, University of Bradford, Bradford, UK.

4. In 1985, I joined the faculty at the University of Minnesota, College of Pharmacy as an Assistant Professor. I was promoted to Associate Professor in 1992, to Director of Graduate Studies in 1994 (until 1998), and to Full Professor in 1999. In 2006, I was appointed the William and Mildred Peters Endowed Chair in the Department of Pharmaceutics. In 2024, I was appointed the Head of the Department of Pharmaceutics.

5. As a professor, I have supervised about 30 graduate student Ph.D. theses and mentored numerous postdoctoral scholars. I have supervised and directed the work of students and scholars in the field of pharmaceutical sciences.

6. Over the course of my career, I have been honored with a multitude of fellowships, awards, and recognitions. I've received the Young Investigator Award twice, from the American Association of Colleges of Pharmacy and Lilly Research Laboratories. Additionally, I've been awarded the Morse-Alumni Award for Outstanding Contributions to Undergraduate Education and Award for Outstanding Contributions to Graduate and Professional Education, both from the University of Minnesota. In 1999, I was inducted into the University of Minnesota's Academy of Distinguished Teachers. The following year, I was elected to the "Excipients: Test Methods Expert Committee" by the United States Pharmacopeia Council of

Experts (“USP Council of Experts”). The USP Council of Experts and its Expert Committees are responsible for developing and revising standards for drugs and excipients in the United States Pharmacopeia and the National Formulary (USP–NF). These contain the quality standards for active pharmaceutical ingredients, drug products, and excipients. In 2010, I received the American Association of Pharmaceutical Scientists (AAPS) Outstanding Educator Award, recognizing excellence in education in the technologies related to pharmaceuticals. This was followed by the PhRMA (Pharmaceutical Research and Manufacturers of America) Foundation Award in Excellence in 2013. Recently, in 2021, I was honored with the Michael J. Pikal Distinguished Scholar Award in Pharmaceutical Processing, by the National Institute for Pharmaceutical Technology & Education (NIPTE).

7. I have authored over 200 research articles that have been published in peer-reviewed journals and have contributed to ten different book chapters in the fields of pharmaceutical sciences. I am also an inventor on three patents and patent applications, including one focused on a resuscitation composition.

8. I have presented more than 250 lectures, seminars, and conferences at invited sessions and symposiums and at professional meetings. Many of my published and presented works relate to the broad area of pharmaceutical sciences.

9. I have been a member of scientific advisory boards of a number of organizations, including the AAPS where I served on the AAPS Fellows Selection

Committee and chaired the AAPS Preformulation Section Focus Group. I am also currently serving as a member of the International Pharmaceutical Excipients Council (“IPEC”) Foundation Scientific Advisory Committee & Selection Committee. I have served in the past or currently serve on the editorial advisory boards of numerous publications, including Pharmaceutical Development and Technology, Molecular Pharmaceutics, and Journal of Pharmaceutical Sciences. I served as an Associate Editor of Molecular Pharmaceutics (published by the American Chemical Society) during 2024. In addition, I have served as a reviewer for journals, including Crystal Growth & Design, Pharmaceutical Research, International Journal of Pharmaceutics, Journal of Pharmaceutical and Biomedical Analysis, among others.

10. A complete listing of my qualifications, experience, publications, and professional activities is set out in my *curriculum vitae* (Ex-1016).

11. I am being compensated for my work in this proceeding at a rate of \$700 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this proceeding.

12. The bases for my opinions are set forth in this declaration.

III. MATERIALS CONSIDERED

13. My analysis in this declaration is based on my knowledge and experience with pharmaceutical sciences, including several years developing and

researching pharmaceutical formulations. Based on my above-described qualifications in Section II, the Patent Trial and Appeal Board should consider me to be an expert in the field. Also, based on my experiences detailed above, I understand and know of the capabilities of persons of ordinary skill in this field.

14. In preparing this declaration, I reviewed the materials in **Appendix A**, including the '076 Patent (Ex-1001); its prosecution history (Ex-1002); provisional application No. 62/903,511 (the "'511 application," Ex-1003); non-provisional Application No. 17/025,881 (the "'881 application," Ex-1004)^{1,2}; continuation-in-part Application No. 17/854,914 (the "'914 CIP application", Ex-1007).

15. Although this declaration refers to selected portions of the cited references, it should be understood that these are examples, and that one of ordinary skill in the art would have viewed the references cited herein in their entirety and in combination with other references cited herein or cited within the

¹ The '511 application and the '881 application are collectively referred to in this declaration as the "Original Applications."

² I understand from my review of the prosecution history and Petitioner's counsel that the '881 application eventually published as U.S. Publication No. 2021/0085608 A1 (the "'608 Publication," Ex-1005) on March 25, 2021 and issued as U.S. Patent No. 11,406,598 (the "'598 Patent," Ex-1006) on August 9, 2022.

references themselves as necessary. The references used in this declaration, therefore, should be viewed as being incorporated herein in their entireties.

IV. LEVEL OF ORDINARY SKILL IN THE ART

16. I was asked to opine on the experience and level of skill of a person of ordinary skill in the art (“POSA”) of the ’076 Patent as of September 20, 2019³ (which I will abbreviate as “2019”) and June 30, 2022⁴ (which I will abbreviate as “2022”).

17. In my opinion, a POSA as of 2019 or 2022 would have a Master’s degree or Ph.D. in pharmaceutical sciences or a related field, along with several years of experience developing and/or researching pharmaceutical formulations, including experience with lyophilization, injectables, and identification of stability issues associated with lyophilized pharmaceutical compositions. A POSA would also understand that the process of drug product development generally involves a

³ I understand from Petitioner’s counsel that September 20, 2019 is the filing date of the ’511 application, the provisional application to which the ’076 Patent, on its face, claims earliest priority. Exs. 1001; 1003.

⁴ I understand from Petitioner’s counsel that June 30, 2022 is the filing date of the ’914 CIP application, the application to which the ’076 Patent, on its face, also claims priority. Exs. 1001; 1007.

multidisciplinary approach and would have had access to and would have consulted with a collaborative team of ordinarily skilled artisans having specialized skills in various aspects of drug development to solve any given problem. For example, a POSA would have the ability, if necessary, to consult with drug formulators, and experts with advanced degrees and/or experience in toxicology, analytical chemistry, process chemistry, formulation science, regulatory affairs, medicine, chemical engineering, pharmacology, and pharmaceuticals, including preclinical and clinical research. Additionally, a POSA would refer to journals, books, regulatory-related submissions, product labels, monographs, patents, and other literature related to the field of pharmaceutical sciences, including without limitation concerning phenobarbital sodium, and would be familiar with developments reported therein.

V. RELEVANT LEGAL STANDARDS

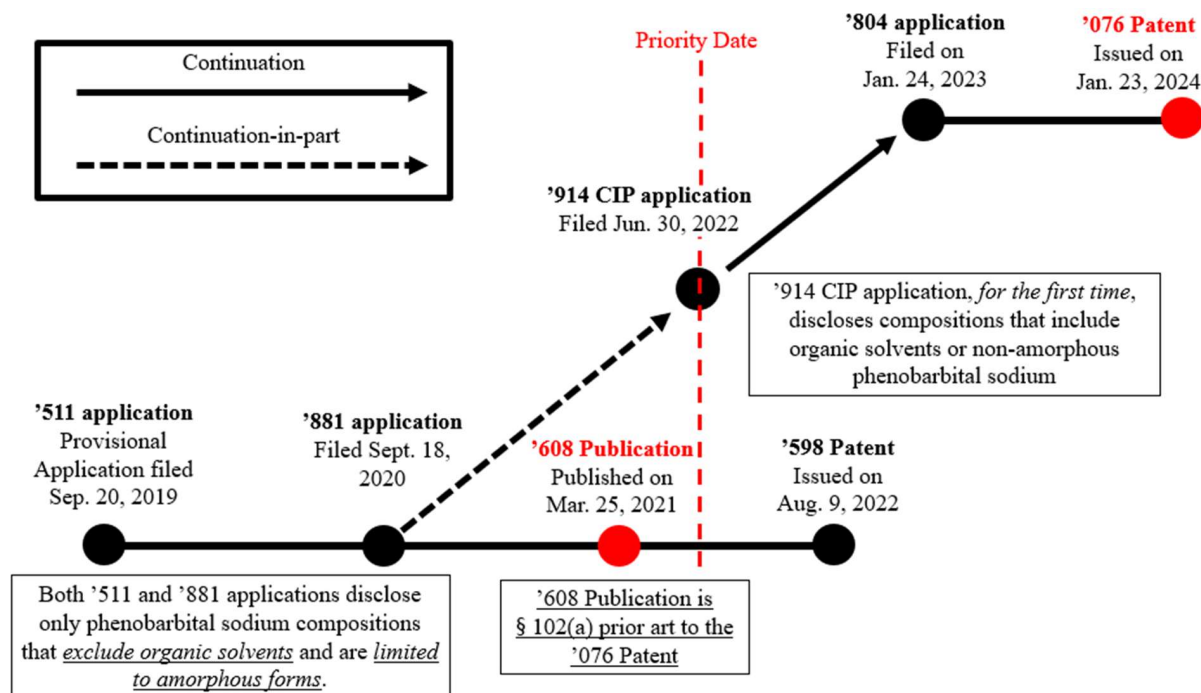
18. In rendering my analysis in this declaration, Petitioner's counsel has informed me about certain aspects of U.S. patent law that are relevant to my opinions. The legal principles provided to me by Petitioner's counsel are in **Appendix B**. I have applied those principles in arriving at my conclusions expressed in this declaration.

VI. OVERVIEW OF THE '076 PATENT

19. The '076 Patent is titled “Lyophilized compositions of phenobarbital sodium salt” and lists on its face five inventors: Bala Tripura Sundari Chodavarapu, Thirupathi Mangali, Jay Shukla, Anand Shukla, and Dasaradhi Lakkaraju.

20. The '076 Patent issued on January 23, 2024, from Appl. No. 18/100,804 (the “'804 application,” Ex-1002) filed on January 24, 2023, and published on May 25, 2023, as US 2023/0157959 A1. Ex-1001 at 1. I understand, from the face of the '076 Patent, that the '804 application is a continuation application of the '914 CIP application, filed on June 30, 2022, which is a continuation-in-part of the '881 application, filed on September 18, 2020, which purports to claim priority to the '511 application, filed on September 20, 2019. Ex-1001 at 1.

21. A schematic of the '076 Patent family tree is provided below:



A. Summary of the '076 Patent and the Challenged Claims

22. Claims 1 and 7 are independent claims. Claims 2-6 and 14-16 depend from independent claim 1 and therefore includes all the limitations of claim 1. Claims 8-13 and 17-20 depend from independent claim 7 and therefore include all the limitations of claim 7.

23. I have broken these claims into several elements to simplify my analysis in this declaration. The claims are also reproduced in **Appendix C**, divided into individual limitations for ease of analysis. The dependent claims include all the features and limitations of the independent claims.

24. Independent claim 1 recites:

[1pre] A storage stable pharmaceutical product, comprising:

[1a] a single use dose vial, and

- [1b]** a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,
- [1c]** wherein the composition is sterile and lyophilized, and
- [1d]** wherein the composition comprises no less than 98% phenobarbital sodium.

Ex-1001 at 59:27-34.

25. Dependent claim 2 recites:

- [2pre]** The pharmaceutical product of claim 1,
- [2a]** wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

Ex-1001 at 59:35-40.

26. Dependent claim 3 recites:

- [3pre]** The pharmaceutical product of claim 1,
- [3a]** wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.

Ex-1001 at 59:41-46.

27. Dependent claim 4 recites:

- [4pre]** The pharmaceutical product of claim 1,

[4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

Ex-1001 at 59:47-53.

28. Dependent claim 5 recites:

[5pre] The pharmaceutical product of claim 1,

[5a] wherein the composition is amorphous.

Ex-1001 at 59:54-55.

29. Dependent claim 6 recites:

[6pre] The pharmaceutical product of claim 1,

[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).

Ex-1001 at 59:56-61.

30. Independent claim 7 recites:

[7pre] A pharmaceutical product, comprising:

[7a] a single use dose vial, and

- [7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,
- [7c] wherein the composition is sterile and lyophilized,
- [7d] wherein the composition comprises no less than 98% phenobarbital sodium, and
- [7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).

Ex-1001 at 59:62-60:8.

31. Dependent claim 8 recites:

- [8pre] The pharmaceutical product of claim 7,
- [8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.

Ex-1001 at 60:9-14.

32. Dependent claim 9 recites:

- [9pre] The pharmaceutical product of claim 7,
- [9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and

then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

Ex-1001 at 60:15-22.

33. Dependent claim 10 recites:

[10pre] The pharmaceutical product of claim 7,

[10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

Ex-1001 at 60:23-29.

34. Dependent claim 11 recites:

[11pre] The pharmaceutical product of claim 10,

[11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

Ex-1001 at 60:30-37.

35. Dependent claim 12 recites:

[12pre] The pharmaceutical product of claim 7,

[12a] wherein the composition is amorphous.

Ex-1001 at 60:38-39.

36. Dependent claim 13 recites:

[13pre] The pharmaceutical product of claim 12,

[13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

Ex-1001 at 60:40-46.

37. Dependent claim 14 recites:

[14pre] The pharmaceutical product of claim 1,

[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

Ex-1001 at 60:47-55.

38. Dependent claim 15 recites:

[15pre] The pharmaceutical product of claim 14,

[15a] wherein the composition is amorphous.

Ex-1001 at 60:56-57.

39. Dependent claim 16 recites:

[16pre] The pharmaceutical product of claim 1,

[16a] wherein the product comprises the 100 mg dose in the single use dose vial.

Ex-1001 at 60:58-60.

40. Dependent claim 17 recites:

[17pre] The pharmaceutical product of claim 7,

[17a] wherein the product comprises the 100 mg dose in the single use dose vial.

Ex-1001 at 60:61-63.

41. Dependent claim 18 recites:

[18pre] The pharmaceutical product of claim 8,

[18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

Ex-1001 at 60:64-61:3.

42. Dependent claim 19 recites:

[19pre] The pharmaceutical product of claim 8,

[19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and

then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

Ex-1001 at 61:4-10.

43. Dependent claim 20 recites:

[20pre] The pharmaceutical product of claim 8,

[20a] wherein the composition is amorphous.

Ex-1001 at 61:11-13.

44. Claims 1-20 of the '076 Patent are directed to “compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water.” Ex-1001 at 1:18-21.

45. The '076 Patent discloses prior art phenobarbital sodium compositions, noting that “[t]he stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products,” such as “phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG).” Ex-1001 at 1:41-2:41. The '076 Patent further highlighted that “these degradation impurities are toxic and cause severe side effects.” *Id.* at 1:60-61. The '076 Patent disclosed that the prior efforts to “decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation focused on minimizing the total amount of water to reduce the hydrolysis and consequently

the formation of the degradation products.” *Id.* at 2:4-18. While the amount of impurities decreased, “impurities such a PEAU [were] still present in undesirable amounts, particularly after extended storage.” *Id.* at 2:20-24.

46. The '076 Patent discloses “compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation,” and “[t]he contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity” that “may include no less than 98% Phenobarbital Sodium.” Ex-1001 at 2:45-52. The '076 Patent noted that “[t]he quantity of undesirable and/or toxic degradation impurities that are produced from this [disclosed] formulation are less than those in current commercial product.” *Id.* at 2:55-59.

47. The '076 Patent discloses that “the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg.” Ex-1001 at 4:65-67, 16:44-46. It states that the “disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates.” *Id.* at 11:59-62. The '076 Patent further discloses that “[t]he lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose” and that “the reconstituted solution has no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or

PBG.” *Id.* at 11:56-59, 4:49-53. For example, the ’076 Patent notes that “the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration.” *Id.* at cols. 13-14; *see also id.* at Tables 2-3.

48. Tables 7-9, 13, and 16 of the ’076 Patent illustrate the stability data of pharmaceutical products covered by claims 1-20. Ex-1001 at Tables 7-9, 13, 16. The ’076 Patent further discloses the results of “extended stability studies,” showing that “the lyophilized amorphous phenobarbital had a storage stability at 25° C. and 60% relative humidity for up to and beyond three years and did readily dissolve upon reconstitution.” *Id.* at 29:61-30:59, Tables 18-23.

49. The ’076 Patent also discloses stability results for phenobarbital sodium reconstituted with dextrose, saline, and water. *Id.* at Tables 24-28.

50. The ’076 Patent further teaches that “[i]n further experiments, the inventors investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents. To that end, the inventors tested isopropanol, tert-butanol, ethanol, and acetonitrile as co-solvents.” Ex-1001 at 51:30-36; *see also id.* at Tables 31-33. The ’076 Patent discloses that “although no known degradation products were observed above quantitation limit, the residual solvents could not be

removed completely after lyophilization” and because “organic solvents are toxic to all age groups, . . . the lyophilized product with only water as solvent is preferred over formulations containing any organic co solvents.” *Id.* at 57:60-58:33.

51. Tables 15 and 30 of the '076 Patent describe the lyophilization cycle parameters. Ex-1001 at Tables 15, 30.

52. The '076 Patent also provides X-ray powder diffraction (XRPD) pattern of phenobarbital sodium products covered by claims 1-20 and discloses that the claimed lyophilized pharmaceutical products are “amorphous” and “non-crystalline unlike the USP grade P API.” Ex-1001 at Figs. 5B-5D, 11:52-56.

B. Prosecution History of the '076 Patent

53. The '076 Patent issued from the '804 application, filed on January 24, 2023. The '804 application had twenty application claims, with application claim 1 as the sole independent claim. Ex-1002 at 160-62. Application claim 1 of the '804 application originally recited as follows:

1. A pharmaceutical product, comprising:

a container enclosing a single dose of lyophilized phenobarbital sodium powder;

wherein the phenobarbital sodium powder optionally contains residual quantities of tert-butanol, isopropanol, ethanol, or acetonitrile and wherein the phenobarbital sodium powder otherwise does not contain an organic solvent or preservative; and

wherein the phenobarbital sodium powder is storage-stable.

Ex-1002 at 160.

54. The Examiner initially rejected application claims 1-20 as obvious over U.S. Patent Application Publication No. US 2017/0143719 (“Parker”)⁵ in view of *Lyophilization of Parenteral (7/93): Guide to Inspection of Lyophilization of Parenterals*, U.S. FOOD AND DRUG ADMINISTRATION (1993), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793> (“FDA_7/93”). Ex-1002 at 270-71. The Examiner reasoned that it would have been within the ordinary skill of the art to claim a stable product as taught by Parker while incorporating the water content, humidity, and temperature parameters from FDA_7/93, with a reasonable expectation of achieving similar shelf stability. *Id.* at 271.

55. On September 20, 2023, the Applicant had an interview with the Examiner, highlighting that neither Parker nor FDA_7/93 disclosed a concentration

⁵ There appears to be a typographical error in the citation to Parker within the Office Action. The correct citation can be found in the *Notice of References Cited* for Appl. No. 18/100,804, dated June 23, 2023. *See also* Ex-1002 at 267-68, 273.

of no less than 98% phenobarbital sodium or the specific conditions required to achieve such results. Ex-1002 at 294. The Applicant proposed new claims incorporating these limitations. *Id.* Following the interview, the Applicant canceled claims 1-20 and submitted new claims 21-33. *Id.* at 284-87. The newly proposed claims did not require limitations related to organic solvents or preservatives but in their revised state were broad enough based on their plain language to encompass compositions containing organic solvents or preservatives. *Id.* at 285-87.

56. During prosecution, the Applicant acknowledged that Parker addresses the stability of phenobarbital sodium in an injectable solution but does not involve lyophilization. Ex-1002 at 288-89. Moreover, the Applicant argued that Parker provides no motivation to modify its formulation, as the stability problem in Parker was already solved. *Id.* The Applicant further contended that lyophilizing Parker's formulation would not yield a composition containing no less than 98% phenobarbital sodium because Parker's formulations include stabilizing co-solvents such as glycols (e.g., propylene glycol) and C1-C4 alcohols (e.g., ethanol) in amounts exceeding the phenobarbital sodium content. *Id.* at 289. Additionally, since glycols are not volatile under lyophilization conditions, they would remain in the final product. *Id.* The Applicant also emphasized that lyophilization processes and conditions (e.g., temperature, pressure, and duration for freezing, primary drying, and secondary drying) can significantly affect the physicochemical properties of the

lyophilized product. *Id.* Because FDA_7/93 does not provide guidance on which lyophilization parameters would lead to the claimed composition, the Applicant argued that it fails to support the Examiner's rejection. *Id.* at 289-90.

57. The Examiner ultimately allowed claims 21-33, concluding that neither Parker nor FDA_7/93 discloses the amount of phenobarbital, the reaction conditions to form it, or its amorphous property. Ex-1002 at 296. Following the Notice of Allowability, the Applicant submitted an amendment under 37 C.F.R. § 1.312 to introduce additional claims, which either combined previously allowed dependent claims or further narrowed the independent claims. *Id.* at 347. After considering and entering the amendment, the Examiner allowed claims 21-40 to issue. *Id.* at 355-56, 361.⁶

VII. BACKGROUND ON THE TECHNOLOGY OF THE '076 PATENT AND THE STATE OF THE ART

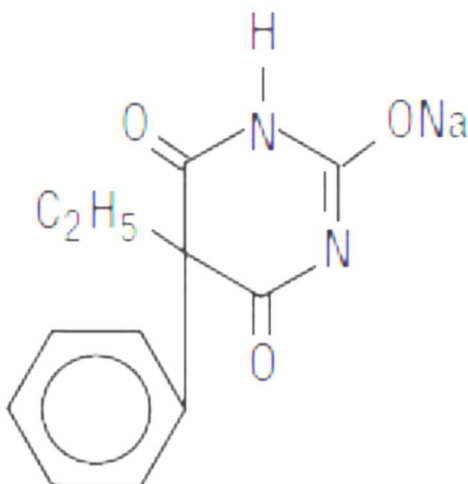
58. Below is a summary of the concepts of pharmaceutical science and lyophilization that are relevant to my opinions set forth in this declaration.

⁶ While the Corrected Notice of Allowability for Appl. No. 18/100,804, dated December 15, 2023, states that the allowed claims are 1-40, the issued '076 Patent contains only twenty claims. *See* Ex-1002 at 355-56; Ex-1001 at cls. 1-20.

A. Phenobarbital Sodium and Its Harmful Degradants

59. As of 2019, phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$), the sodium salt of phenobarbital, was recognized as a drug with anticonvulsant, and hypnotic effects, widely used in medical practice around the world. Ex-1009⁷ at 4, 42-43.

Phenobarbital preparations had been vital medicines for over 50 years, reflecting their established role in healthcare. *Id.* at 4. Chemically identified as 2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione,5-ethyl-5-phenyl-, monosodium salt, phenobarbital sodium has the following structural formula:



Ex-1013. Its efficacy, particularly in treating status epilepticus, were extensively supported and acknowledged by medical and pharmaceutical authorities. *See*

⁷ I understand from the Declaration of Ryan Bernasch (Ex-1010) that Ex-1009 is a certified English translation of Ex-1008. For ease of reference, the translated Ex-1009 is cited throughout to reference the original PIF publication (Ex-1008).

generally Ex-1009. For decades, phenobarbital sodium has been used to manage seizure disorders, with its effectiveness reinforced by significant clinical experience and regulatory approval. *Id.*

60. As of 2019, the physical and chemical properties of phenobarbital sodium were extensively documented. The compound appears as white crystalline granules or flaky crystals and is characterized by its high solubility in water, slight solubility in 95% ethanol, and is almost insoluble in diethyl ether, chloroform, and dichloromethane. Ex-1009 at 6; Ex-1013. Phenobarbital sodium is also hygroscopic, meaning it readily absorbs moisture from the air, and it decomposes slowly when exposed to moist air. Ex-1009 at 6; Ex-1017 at 7; *see also id.* at 10-11. Despite its critical role in medicine, phenobarbital sodium is challenging to dissolve in organic solvents, even when aggressive mixing techniques are applied. Ex-1012 at [0005]. Its solubility in ethanol and other solvents is limited, with reports indicating that it only dissolves to a concentration as high as 100 mg/mL in ethanol. *Id.*

61. One of the critical challenges associated with phenobarbital sodium is its susceptibility to degradation, particularly in the presence of water. Ex-1009 at 6; Ex-1017 at 7, 10-11; Ex-1012 at [0004], [0006], [0007], Table 1; Ex-1005 at Abstract, [0006]-[0007], [0017], [0023], [0073]. Phenobarbital sodium is prone to hydrolysis, where hydroxyl ions initiate a degradation process that breaks down the

phenobarbital ring structure, resulting in the formation of harmful degradation products such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPM), and alpha-phenylbutyrylguanidine (PBG). Ex-1012 at [0004], [0006], [0007], Table 1; *see also* Ex-1009 at 12. Other degradation products can be formed under other conditions such as exposure to basic conditions, oxidation, and heat. Ex-1012 at [0007]. The degradation of phenobarbital sodium is a well-recognized issue in pharmaceutical formulations, with significant implications for the long-term stability and safety of pharmaceutical products containing this compound.

B. Active Pharmaceutical Ingredients and Pharmaceutical Compositions and Strategies for Impurity Control

62. An active pharmaceutical ingredient (“API”) is the primary component in a pharmaceutical composition that produces the intended therapeutic effects. It is the therapeutically active substance that interacts with the body to diagnose, treat, cure, or prevent diseases. In drug formulations, the API is typically combined with “inactive” ingredients, known as excipients, which aid in the drug’s delivery, stability, and absorption. The quality, purity, and potency of an API are critical, as they directly influence the safety and efficacy of the final pharmaceutical product. According to the International Conference on Harmonisation (“ICH”) Guidelines, an impurity is defined as “any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances.” Ex-1018 at 1. This

definition also applies to drug products, where “extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties.” *Id.* Furthermore, “[t]he impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention.” *Id.*

63. Pharmaceutical compositions, also referred to as formulations, are designed to deliver medicinal agents effectively. These compositions can have different drug concentrations to address specific treatment requirements and are commonly available in single-use or multi-use packaging. Single-use formulations for parenteral medications are preferred whenever possible, as it minimizes the risk of contamination and reduces the potential for infection. Ex-1019 at 45. Contamination risks, including outbreaks of HBV and HCV, have been linked to practices such as reinserting used needles into multi-dose vials or solution containers and using single needles or syringes for multiple patients. *Id.* These risks highlight the importance of adhering to aseptic techniques, including the use of sterile, single-use needles and syringes for each injection and avoiding contamination of equipment and medications. *Id.* Multi-dose formulations, on the other hand, typically contain antimicrobial preservatives to help prevent contamination during repeated use. Ex-1020 at 6-7.

64. The manufacturers of parenteral products focus on sterility, as sterility is an absolute requirement for these products, regardless of formulation type. Ex-1021 at 8. This requirement must be a primary consideration from the earliest stages of formulation and process development to produce an optimized sterile product. *Id.* Parenteral products are typically sterilized by filtration or terminal sterilization methods, with filtration being the most common approach despite regulatory preferences for terminal sterilization. *Id.* at 13, 25-26.

65. Pharmaceuticals can exist in crystalline, amorphous or partially crystalline forms. The crystalline state is characterized by a long-range periodicity in molecular arrangement, while amorphous forms lack this long-range order and exhibit a disordered structure. Amorphous forms typically demonstrate higher solubility and faster dissolution rates compared to crystalline forms, potentially enhancing the bioavailability of certain drugs. Analytical techniques such as differential scanning calorimetry and X-ray diffractometry are used to study and differentiate these physical states, offering insights into the stability and performance of pharmaceutical products.

66. Process chemists and engineers emphasize the importance of controlling impurities and preventing degradation during production and storage to maintain the safety and efficacy of APIs and pharmaceutical compositions. Degradation can generate harmful byproducts, and impurities can arise from

synthetic processes, storage conditions, packaging materials, excipients, or contamination. Ex-1018 at 1-2. APIs and pharmaceutical compositions may degrade through hydrolysis, oxidation, or heat exposure. *Id.* at 1-3; *see also* Ex-1012 at [0004]-[0007], Table 1. In solids, hydrolysis occurs when water triggers chemical reactions that break down the API, with water potentially originating from residual moisture in the composition or atmospheric humidity. Oxidative degradation involves the interaction of the API with oxygen, which can diminish the drug's effectiveness. "The presence of impurities can complicate purifications and decrease isolated yields," necessitating optimization to minimize impurity formation. Ex-1022 at 186.

67. Effective strategies to control impurities and drug degradation in pharmaceutical compositions are crucial for ensuring safety and efficacy. Impurity management begins with proactive measures, including the selection of alternative reagents, starting materials, or synthetic routes that introduce potential impurities early in the process, allowing for easier removal. Ex-1023 at 385-87, Table 13.8. Controlling impurities involves setting impurity specifications at intermediate stages, conducting forced degradation studies to predict potential impurities, and developing analytical methods to monitor and mitigate their presence throughout the manufacturing process. Ex-1022 at 279-80. Expelling impurities focuses on purification and isolation techniques, ensuring that the final product meets rigorous

safety and efficacy standards. Ex-1023 at 385-87. These principles form the foundation of the ACE strategy—“Avoid, Control, and Expel”—which offers a comprehensive framework for managing impurities. *Id.*

68. Accurate monitoring and qualification of impurities are important. Ex-1018 at 3. Qualification involves acquiring and evaluating data to confirm the biological safety of impurities. *Id.* Criteria for qualification include ensuring impurity levels do not exceed those observed in FDA-approved drugs or justifying their levels through scientific literature or genotoxicity studies. *Id.* at 4. The ICH guidelines provide thresholds to guide impurity qualification and maintain pharmaceutical safety. *Id.* at 4, Tables 3-4.

69. Process optimization is equally vital for managing impurities. Early establishment of routine impurity profiles helps minimize rework, saving time and resources. Ex-1022 at 279-80. Once the structures of impurities are identified, “developing procedures to minimize key impurities in a drug substance is generally straightforward,” and the mechanisms behind their formation can often be elucidated, enabling adjustments to prevent their generation. *Id.* at 200, 280. The primary goal of process optimization is to maximize product yield while minimizing by-products. *Id.* at 186. “Impurities in a final product must be known and controlled” because failing to do so compromises drug substance quality and patient safety. *Id.* at 277.

70. From both an economic and ethical perspective, controlling impurities is paramount. “The economics of failing to control the physical form and impurities in APIs provide good reasons to monitor operations and scrutinize data[, and] from a moral standpoint we must control the impurities in APIs.” Ex-1023 at 390. Through the integration of strategies such as impurity profiling, process optimization, and adherence to regulatory guidelines, manufacturers can ensure pharmaceutical compositions remain safe, effective, and of the highest quality.

C. Lyophilization of Pharmaceutical Products

71. Lyophilization, also known as freeze-drying, is a vital process in the pharmaceutical industry, designed to remove water from pharmaceutical products through a controlled sequence of freezing, sublimation, and desorption. This method ensures product stability, extends shelf life, and facilitates reconstitution. Ex-1021 at 17; Ex-1024 at 1-2; Ex-1025 at 20.

72. The process begins by dissolving the drug and excipients in a suitable solvent, typically water for injection (WFI), which is sterilized and filled into sterile containers such as glass vials or ampoules under aseptic conditions. Ex-1024 at 2, 8; Ex-1026 at 54-55. These containers are then partially stoppered and placed in the lyophilizer. Ex-1024 at 2, 8. The freezing phase follows, where the solution is cooled to temperatures as low as -40°C or below, immobilizing components, minimizing thermal degradation, and separating solutes from the

solvent through ice crystallization. Ex-1021 at 17; Ex-1026 at 54-55; Ex-1025 at 20-21; Ex-1027 at 17, 31, 69. The freezing phase “separate[s] the solvent from the solutes,” “minimize[s] thermal degradation,” “immobilize[s] [*sic*] the components in the solution,” and “prevent[s] product foaming when vacuum is applied.” Ex-1024 at 3.

73. Once frozen, the primary drying stage begins. In this phase, the ice is removed through sublimation under reduced pressure. Ex-1021 at 17; Ex-1024 at Abstract, 1-2, 4-5; Ex-1026 at 54; Ex-1027 at 18, 31; Ex-1025 at 22-23. This stage requires precise control of pressure and temperature to avoid melt-back, particularly for amorphous products, and typically achieves low residual moisture levels. Ex-1021 at 17; Ex-1024 at 4-5; Ex-1026 at 54; Ex-1027 at 18, 31; Ex-1025 at 23. Following the removal of ice, secondary drying desorbs bound water by gradually increasing the shelf temperature, ensuring further reduction in water content without compromising the product’s physical integrity. Ex-1021 at 17; Ex-1024 at 5; Ex-1026 at 54; Ex-1027 at 18, 31, 466; Ex-1025 at 23.

74. Lyophilization offers several significant advantages over other drying methods. By maintaining low moisture levels, it minimizes chemical degradation and microbial growth, conferring long-term stability and sterility of the product. Ex-1024 at Abstract; Ex-1026 at 55; Ex-1027 at 97, 257. The sterile filtration of solutions before freeze-drying, combined with aseptic processing and stoppering

within the freeze dryer, substantially reduces contamination risks. Ex-1026 at 55; Ex-1027 at 273, 284. Furthermore, the process protects thermally sensitive drugs from degradation and prevents oxidative denaturation by sealing products under vacuum or inert gas. Ex-1024 at 2.

75. This process is particularly beneficial for pharmaceuticals intended for parenteral administration, including chemical compounds, vaccines, and biologics, as it preserves sterility, enhances dissolution rates, and facilitates rapid reconstitution. Ex-1024 at 1, 6, Table 1; Ex-1026 at 5; Ex-1027 at 284, 456. Additionally, POSAs know that lyophilization is often used to convert a crystalline drug to an amorphous state. Ex-1025 at 2; Ex-1028 at 4-5; Ex-1029 at 227; Ex-1030 at 273; Ex-1031 at Abstract, 3. When compared with the crystalline state, the amorphous form generally exhibits enhanced solubility and dissolution. Ex-1031 at 2; Ex-1028 at 3-5; Ex-1032; Ex-1030 at 272; Ex-1033 at 5-6; Ex-1025 at 2.

76. The ability to precisely control residual water content in the lyophile and gas composition in the headspace during sealing may be critical for ensuring product quality and stability. Lyophilization not only provides a robust method for stabilizing sensitive pharmaceuticals but also addresses the sterility requirements. Ex-1021 at 17; Ex-1027 at 257. By effectively removing water and maintaining aseptic conditions, lyophilization remains an indispensable unit operation in modern pharmaceutical manufacturing. Ex-1021 at 17; Ex-1027 at 456.

D. Storage Conditions and Stability Testing

77. Stability testing is a critical component of pharmaceutical development, aimed at ensuring that drug substances and products maintain their intended quality, safety, and efficacy throughout their shelf life. Ex-1034 at 5, 7, 13-14, 16-18; *see also* Ex-1035 at 4-5, 8-9; Ex-1036 at 5. It is conducted under standardized conditions, such as specific temperature, relative humidity (“RH”), and time parameters, to provide reliable data on likely degradation products, and these studies help establish appropriate storage conditions, retest periods, and shelf lives for drug products. Ex-1035 at 2, 4; Ex-1036 at 5-6.

78. Testing is typically conducted across three categories of storage conditions: long-term, intermediate, and accelerated for APIs and finished products:

For Active Pharmaceutical Ingredients

2.1.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as described in point 2.1.7
Intermediate ^b	30 °C ± 2 °C/65% RH ± 5% RH	6 months

Table continued

Study	Storage condition	Minimum time period covered by data at submission
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored (see "Long-term stability testing conditions as identified by WHO Member States"). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH for zone II.

^b If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

For Finished Pharmaceutical Products

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as referred to in section 2.2.7
Intermediate ^b	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Ex-1034 at Tables 2.1.7.1, 2.2.7.1; *see also* Ex-1035 at 4, 7; Ex-1036 at 7-10, 12-17. These standardized conditions ensure comprehensive data that supports storage recommendations. *See id.*

79. The frequency of testing during stability studies varies depending on the proposed shelf life of the product. For products with a shelf life of 12 months or more, testing is generally conducted every three months during the first year, every six months during the second year, and annually thereafter. Ex-1034 at 7, 16;

Ex-1035 at 4, 8; Ex-1036 at 7, 12. This schedule ensures a robust stability profile and provides sufficient data to address storage, shipment, and subsequent use of the product. *See id.*

80. Comprehensive evaluations under standardized conditions extend beyond the finished drug product to include assessments of stability after reconstitution or dilution, ensuring the medication remains safe, effective, and consistent with labeled specifications at the time of administration. Ex-1035 at 7-9. For lyophilized drugs, reconstitution is routinely performed using appropriate volume of water for injection (WFI) or another suitable aqueous solution volume, such as 10 mL, as this is a convenient and sufficient volume for fully dissolving the drug product and ensuring reliable stability assessments, depending on the specific drug and its requirements. *See, e.g.,* Ex-1037 at 1-4, 9; Ex-1038 at 2; Ex-1039 at 2:39-50, 5:21-25, 5:31-34, 5:46-55, 7:22-30, 10:47-55, 11:28-30, 11:41-44, 12:29-31, 12:54-64, 13:4-14, 14:35-39, 14:54-56, 15:7-10, 15:63-66, 16:51-56, 17:2-9, 18:5-10, 21:37-43, 22:45-51, 23:53-59, 24:33-26:9. Using a round number like 10 mL is standard practice, as it simplifies measurements and ensures consistency during stability testing. Stability testing of reconstituted solutions involves analyzing for degradation products, validating the stability profile, and confirming product efficacy under various conditions. High-performance liquid chromatography (HPLC) is frequently employed for these analyses, providing

critical data on degradants over time. Ex-1037 at 1, 3-10; Ex-1038 at 2-3; *see generally* Ex-1039. These studies are vital for supporting accurate labeling and storage instructions.

81. Stability testing also involves stress testing to evaluate the intrinsic stability of the drug substance under extreme conditions, such as elevated temperature, humidity, and light exposure. Ex-1035 at 3-4; Ex-1036 at 6. Stress testing helps establish degradation pathways, identify likely degradation products, and validate the analytical methods used. *Id.*

82. Storage conditions and study designs must consider the characteristics of the API and finished pharmaceutical product. Ex-1034 at 5, 13. Factors such as thermal stability, sensitivity to moisture, and solvent loss are critical in designing stability studies. *Id.* at 16. It is critical to test APIs and finished pharmaceutical products under storage conditions that simulate the climatic environment of target markets. *Id.* This approach ensures that the product remains stable under real-world conditions and supports shelf-life claims. *Id.* at 5, 13, 16.

83. Stability testing under well-defined conditions ensures that pharmaceutical products maintain their intended quality throughout their lifecycle. By simulating storage and use conditions, testing provides the data necessary to guide storage recommendations, reconstitution methods, and shelf-life determinations, ensuring patient safety and product efficacy.

VIII. CLAIM CONSTRUCTION

84. The legal principles relevant to claim construction, as provided to me by Petitioner's counsel, are outlined in **Appendix B**. These legal standards were considered in forming the opinions expressed in this declaration.

85. I understand that, for purposes of my analysis in this *inter partes* review proceeding, the terms appearing in the patent claims should be interpreted according to their "ordinary and customary meaning," which is often referred to as the *Phillips* standard. In determining the ordinary and customary meaning, I understand that the words of a claim are first given their plain meaning that those words would have had to a person of ordinary skill in the art at the time of the alleged invention. I also understand that the structure of the claims, the specification, and file history may be used to better construe a claim. Moreover, I understand that even monographs and dictionaries may be used, albeit under limited circumstances, to determine the meaning attributed by a person of ordinary skill in the art to a claim term.

86. I have been asked by Petitioner's counsel to consider claim construction as of 2019 and 2022. My opinions are the same regardless of which date is used.

87. Here, I have reviewed the claims of the '076 Patent addressed in this proceeding. For purposes of addressing the anticipation and obviousness issues in

this proceeding, the claim elements include straightforward language and are readily understandable according to their ordinary and customary meaning—without the need to inject specialized definitions or substitute terminology. For purposes of comparing the claim elements with the prior art, it is not necessary to resort to definitions or substitute terminology when assessing the Grounds below.

IX. INVALIDITY GROUND 1: THE CHALLENGED CLAIMS ARE OBVIOUS OVER PIF, IN VIEW OF PARKER AND WEST-WARD

88. It is my opinion that the challenged claims would have been obvious as of September 20, 2019, the filing date of the '511 application.

89. The Pharmaceutical Interview Form (“PIF”), revised in July 2010 (Ex-1009 at 1), was publicly available by at least March 13, 2011, well before September 20, 2019. Ex-1011. By 2019, phenobarbital sodium was widely recognized for its anticonvulsant, hypnotic, and analgesic properties, and POSAs knew that numerous formulations of phenobarbital sodium had been approved and made commercially available. *See supra* Section VII.A.

90. A POSA would have been familiar with various phenobarbital sodium products that were already on the market and would have recognized Nobelbar as one of those commercially available products. A POSA would have been particularly interested in it because of its excipient-free injectable formulation designed for safe, intravenous use in neonates. *See, e.g.*, Ex-1040 at 1-2, 5; Ex-

1041 at 6. A POSA would have known that Nobelbar was produced by Nobelpharma Co. Ltd starting in 2008. *See* Ex-1040 at 2, 6; Ex-1041 at 6.

91. A POSA in 2019 interested in phenobarbital sodium products would have as a matter of routine become familiar with Nobelbar by, among other things, consulting the manufacturer's website (www.nobelpharma.co.jp/) to gain further insights into the drug product. The PIF was publicly available from the Nobelpharma's website URL of <http://www.nobelpharma.co.jp/medical/pdf/Nobelbar/interviewform.pdf> before 2019. Ex-1009; Ex-1011. The PIF's availability at this URL in 2011 would have made it readily available to POSAs, and a publication POSAs exercising reasonable diligence would have identified, reviewed, and studied to supplement their knowledge about available phenobarbital sodium products.

92. A POSA would have ordinarily reviewed and relied on the PIF (and information like it) from the drug manufacturers' websites, especially as the PIF is identified as "a source of drug information necessary to interview pharmaceutical company medical representatives . . . and other personnel to evaluate [Nobelbar]" and "a comprehensive drug information manual that supplements information in the package inserts of ethical drugs, and provides pharmacists and other healthcare professionals with information necessary for the proper use and evaluation of drugs, as well as information to support the provision of drug information in their

daily work.” Ex-1009 at Outline of IF Usage Guide; Ex-1011. Accordingly, as I understand from Petitioner’s counsel, PIF qualifies as § 102(a) prior art.

93. Parker, published on May 25, 2017, also predates September 20, 2019, making it, according to Petitioner’s counsel, § 102(a) prior art. Ex-1012 at cover. A POSA interested in investigating a phenobarbital sodium product would have similarly been aware of and studied patents relating to phenobarbital, including Parker as it disclosed a stable formulation of phenobarbital sodium injection.

94. West-Ward, updated in August 2011 (Ex-1013), was publicly available by at least October 4, 2015, prior to September 20, 2019. Ex-1014. A POSA would routinely consult widely accessible and reliable resources, such as the National Library of Medicine (“NLM”), to stay informed of current pharmaceutical products on the market. DailyMed (<https://dailymed.nlm.nih.gov/dailymed/index.cfm>), a website service provided by the NLM, consolidates medication labels submitted to the U.S. Food and Drug Administration and ensures healthcare professionals have convenient online access to official drug label information, including administration instructions, dosages, safety guidelines, and clinical pharmacology details. Through DailyMed’s continuously updated database, a POSA seeking information on phenobarbital sodium products would have ordinarily used and relied on the information contained in that website and would have readily discovered the comprehensive labeling details for various manufacturers. By

entering relevant search terms and filtering by active ingredients or product names, a POSA could locate West-Ward, which was publicly accessible before 2019, and find that phenobarbital sodium products have been sold for several years by West-Ward Pharmaceutical Corp. *See* Ex-1013; Ex-1014. West-Ward was publicly available from the DailyMed's website URL of <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ffcaa218-ed6a-4557-9645-b9a91128a214>. Ex-1013; Ex-1014. POSAs exercising reasonable diligence would have identified, reviewed, and studied West-Ward to supplement their knowledge about available phenobarbital sodium products.

95. In my opinion, the challenged claims are rendered obvious by PIF, in view of Parker and West-Ward, as well as the general knowledge of a POSA.

96. The challenged claims are divided into specific limitations as shown in **Appendix C**.

A. Overview of the PIF

97. PIF discloses Nobelbar, a lyophilized phenobarbital sodium formulation containing “274 mg of phenobarbital sodium (250 mg as phenobarbital)” per vial. Ex-1009 at 1, 7, 38. Nobelbar is a lyophilized injection composed solely of the drug substance, with no additives. *Id.* at 4, 7. According to PIF, manufacturing was approved on October 16, 2008, followed by NHI drug price standard listing on December 12, 2008, and sales started on December 16,

2008. *Id.* at 1. PIF teaches that Nobelbar was Japan's first intravenous phenobarbital preparation approved for neonatal convulsions and status epilepticus. *Id.* at 4. PIF indicates that phenobarbital sodium is noted for its extreme solubility in water and for gradually decomposing when exposed to moist air. *Id.* at 6.

98. Nobelbar's stability was tested under various conditions, evaluating various physicochemical properties including pH, solubility, related substances, moisture content, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, and sterility. *Id.* at 6-7. PIF reports no changes in these test parameters under any storage conditions other than moisture content of the formulations. *Id.* Long-term formulation stability testing was conducted at 25 ± 2 °C / $60 \pm 5\%$ RH for 36 months, while accelerated testing was performed at 40 ± 2 °C / $75 \pm 5\%$ RH for 6 months. *Id.* at 7. For the API, similar storage conditions were used, except long-term testing extended to 60 months. *Id.* at 6.

99. When assessing drug compatibility, Nobelbar was dissolved in 10 mL of saline solution to test the physicochemical stability of Nobelbar when combined with other drugs. *Id.* at 8. PIF also notes that certain related substances, such as PEAU, may be generated during manufacturing. *Id.* at 12.

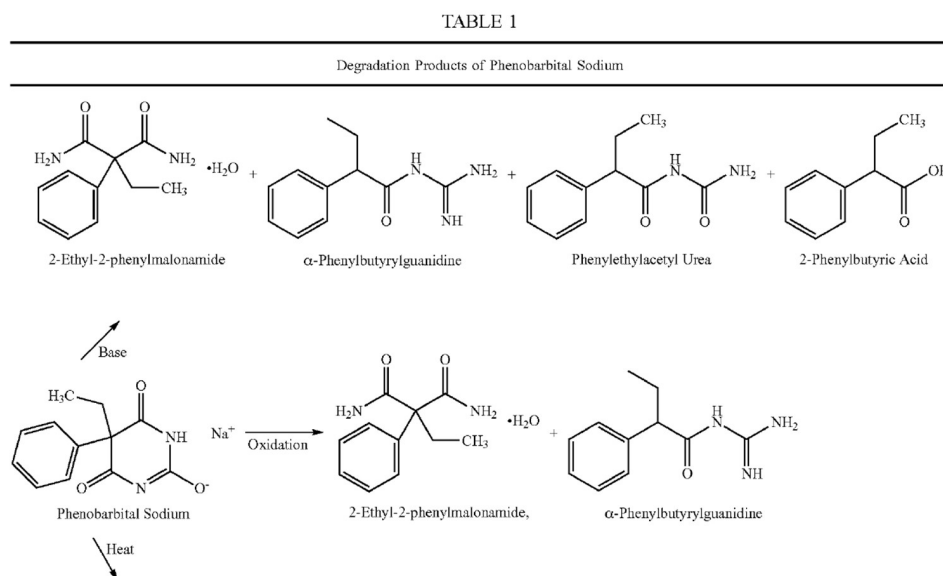
100. The dosage and administration guidelines indicate an initial dose of 20 mg/kg administered intravenously for neonatal convulsions, followed by a

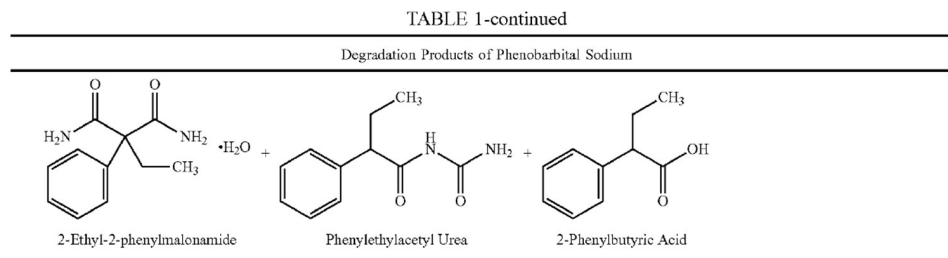
maintenance dose of 2.5-5 mg/kg once daily. *Id.* at 13. For status epilepticus, 15-20 mg/kg once daily is recommended. *Id.*

101. PIF also mentions that 30 mg, 50 mg, 60 mg, or 130 mg per 1 mL phenobarbital sodium injection products were sold in the U.S. *Id.* at 42.

B. Overview of Parker

102. U.S. Patent Application Publication No. US 2017/0143719 (“Parker”), titled “Stable formulation of phenobarbital sodium injection,” describes a stable phenobarbital sodium injection formulation designed to minimize impurity formation during extended storage. Ex-1012 at Title, Abstract, [0017]; [0016]-[0017], [0023], [0029], [0036]. Parker discloses that traditional phenobarbital sodium formulations, typically dissolved in water, are prone to hydrolysis, destroying the phenobarbital ring complex and generating impurities such as PEAU, phenyl butyric acid (PBA), 2EPMM, and PBG:





Id. at [0004]-[0006], [0016], Table 1. Because water accelerates this degradation, Parker's formulation—in dosage amounts of 15 to 200 mg/mL phenobarbital sodium—relies on a minimal amount of water and includes a C1-C4 alcohol (e.g., ethanol) and propylene glycol to stabilize the active ingredient and substantially reduce impurity formation. *Id.* at Abstract, [0017], [0031], [0034], [0039]. The final solution contains no more than 50 mg/mL water, even after pH adjustment. *Id.* at Abstract, [0039].

C. Overview of West-Ward

103. West-Ward discloses commercially available phenobarbital sodium injection products containing 65 mg/mL and 130 mg/mL in 1 mL vials, illustrating established dosage strengths. Ex-1013.

D. Motivation to Combine Ground 1 References with a Reasonable Expectation of Success

104. A POSA in 2019 would have been motivated, with a reasonable expectation of success, to combine PIF, Parker, and West-Ward to make a shelf-stable, highly-pure, sterile, lyophilized, amorphous phenobarbital sodium composition.

105. A POSA in 2019 would have been interested in researching and developing phenobarbital sodium products because, among other reasons, the active ingredient was well-known to successfully treat seizures, including for neonates. At the same time, a POSA would have known that phenobarbital sodium was vulnerable to hydrolytic degradation, which causes the formation of impurities including PEAU, 2EPMM, and PBG. A POSA would know that lyophilization is a well-known technique to minimize the water content, especially for an injectable drug composition, and was routinely used by POSAs to make sterile and amorphous drug products. With this background, it was obvious for a POSA in 2019 to research and develop an improved upon phenobarbital sodium product.

106. By 2019, a POSA would have been aware that PIF discloses Nobelbar, a commercially available shelf-stable, sterile phenobarbital sodium freeze-dried product in Japan, and would know that it is intended for single use. Ex-1009 at 4, 7, 21, 22. Nobelbar contains no additives, and multi-dose formulations typically require antimicrobial preservatives to prevent microbial growth after initial use. *Id.* at 4, 7; *see supra* Section VII.B. A POSA would understand from the absence of preservatives that Nobelbar is intended to be a single-use vial. Moreover, PIF's disclosure that the reconstituted product should be used promptly—within 6 hours—and that related substances increase significantly (from 0.09% to 0.49%) within 24 hours after dissolution further supports that the product is intended for

single-dose administration. Ex-1009 at 7, 8, 34. This is consistent with industry practice, where single-use packaging is preferred to minimize contamination risks and ensure patient safety, particularly in vulnerable populations such as neonates.

107. A POSA would also be motivated to reconstitute Nobelbar (and similar lyophilized phenobarbital sodium products) with an appropriate volume (e.g., 10 mL) of an aqueous solution, such as Water for Injection (WFI), as this is a common and well-established practice for preparing intravenous or intramuscular injections. *See supra* Section VII.D. Standard reconstitution practices ensure consistent dosing and minimize variability in administration.

108. In addition, a POSA would conduct standardized stability testing under well-established conditions to ensure the final product's extended shelf life and quality. This includes evaluating stability at long-term room temperature and humidity conditions (e.g., 25 ± 2 °C / $60 \pm 5\%$ RH) and performing accelerated testing at elevated temperature and humidity conditions (e.g., 40 ± 2 °C / $75 \pm 5\%$ RH) for up to 6 months. *See supra* Section VII.D. Given that Nobelbar reportedly has a three-year shelf life, a POSA would understand that it exhibited stability for at least that duration. Ex-1009 at 38. Such testing intervals and conditions are standard industry practices to establish product robustness, impurity profiles, and overall stability, ensuring the final formulation meets stringent product specifications.

109. Since lyophilized phenobarbital sodium is typically administered intravenously or intramuscularly, a POSA would have been motivated to maximize purity, increase stability, and minimize impurities. Intravenous or intramuscular administration routes demand high purity due to the direct entry of the drug into the bloodstream or muscle tissue, increasing the potential impact of toxic impurities. This concern becomes especially pressing when treating sensitive populations, such as neonates, where even very low amounts of toxic degradants could be detrimental.

110. From Parker, a POSA would understand that phenobarbital sodium can degrade via hydrolysis and other mechanisms, forming harmful degradants such as PEAU, 2EPMM, and PBG. Ex-1012 at [0004]-[0007], Table 1; *supra* Section VII.A. In an effort to make a safe product, a POSA would have been motivated to identify and minimize the content of the degradants. The pharmaceutical industry widely recognizes that impurities in the final drug product must be carefully controlled through careful formulation, packaging, and storage under appropriate conditions. By applying known techniques such as lyophilization to minimize the residual water content, the POSA would mitigate hydrolysis and reduce the propensity for drug degradation. The known feasibility of producing a stable lyophilized phenobarbital sodium product, such as Nobelbar, would reinforce a POSA's confidence in achieving a stable, highly pure, and safe

formulation. Given that Nobelbar is indicated for conditions like neonatal convulsions, the need to maximize drug purity and minimize impurities is even more critical, as any toxic impurities including degradants could cause significant risk with respect to patient safety. Ex-1009 at 1, 4, 13; *see supra* Section VII.B.

111. Moreover, a POSA would understand that any lyophilized phenobarbital sodium product must meet regulatory requirements and relevant pharmacopeial specifications. Regulatory authorities mandate strict controls on impurities, sterility, and stability, for injectable products. Ensuring compliance with these standards is essential to maintain patient safety and therapeutic efficacy.

112. West-Ward demonstrates known phenobarbital sodium dosage strengths of 65 mg/mL and 130 mg/mL, while PIF and Parker disclose other clinically employed and feasible concentrations, including 30 mg, 50 mg, 60 mg, or 130 mg per mL in the U.S., and even broader ranges up to 200 mg/mL. Ex-1013; Ex-1012 at Abstract, [0017], [0031]; Ex-1009 at 42. Building on these established dosages, a POSA would have had a reasonable expectation of success in selecting appropriate single-dose vial amounts within these ranges, including 65 mg, 100 mg, 130 mg, or 200 mg, to meet therapeutic needs and dosing convenience.

113. As Nobelbar is lyophilized and intended for parenteral administration, a POSA would know that its production likely involves sterile filtration and aseptic

processing that maintains purity and ensures the final product's sterility. *See supra* Section VII.C.

114. Additionally, since Nobelbar has no additives (Ex-1009 at 4, 7) and maintains stability, a POSA would understand that the Nobelbar composition is close to or above 98% phenobarbital sodium. This aligns with the POSA's goal to minimize impurities and maintain safety, especially for vulnerable patient populations. A POSA would have known that lyophilization is an effective way to minimize the risk of drug degradation during drying. A POSA would have also, as a matter of routine, known how to modulate lyophilization drying conditions to control the residual solvent content. A POSA would have expected that Nobelbar was already at or approaching 98% phenobarbital sodium and, further, a POSA would have been motivated to and would have had a reasonable expectation of success of reaching at least 98% phenobarbital sodium using standard lyophilization techniques. Ex-1027 at 466.

115. Additionally, given that Nobelbar exists as a lyophilized (freeze-dried) preparation, a POSA would also recognize that the lyophilization process can result in amorphous phenobarbital sodium. *See supra* Section VII.C. The low water content in the lyophilized product helps prevent hydrolysis-induced impurity formation.

116. Taken together, the teachings of PIF, Parker, and West-Ward provide a clear roadmap for a POSA to create a shelf-stable, highly pure, sterile, amorphous lyophilized phenobarbital sodium composition that, upon reconstitution with 10 mL of an aqueous solution, contains minimal concentration of degradation products, including PEAU, 2EPMM, and PBG. Drawing on PIF’s demonstration of a stable, no-additive, single-use lyophilized product (Nobelbar), Parker’s insight into the impact of hydrolysis, and West-Ward’s disclosure of known dosage strengths, a POSA would have been motivated to combine these references. By doing so, the POSA would confidently develop a final composition that aligns with the requirements of the challenged claims, ensuring patient safety, efficacy, and robust long-term stability.

E. Obviousness of Claim 1 — Element by Element Claim Analysis

1. [1pre] A storage stable pharmaceutical product, comprising:

117. As I understand from Petitioner’s counsel and as detailed in **Appendix B**, the preamble generally does not constitute a limitation and therefore does not limit the claims.

118. Regardless, PIF discloses Nobelbar, a lyophilized phenobarbital sodium formulation containing “274 mg of phenobarbital sodium (250 mg as phenobarbital)” per vial. Ex-1009 at 1, 7. PIF also discloses that Nobelbar’s manufacturing was approved on October 16, 2008, followed by NHI drug price

standard listing on December 12, 2008, and sales started on December 16, 2008.

Id. at 1. PIF further discloses that stability studies of Nobelbar have shown “no change” in the drug substance’s and drug formulation’s properties (other than the moisture content of the drug product) over extensive testing periods, including long-term storage tests ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$: 60 and 36 months) and accelerated tests ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, 6 months). *Id.* at 6-7. These tests evaluated various physicochemical properties including pH, solubility, related substances, moisture content, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, and sterility. *Id.* No changes were observed following storage, confirming the stability of the lyophilized product. *Id.* PIF also reports that Nobelbar has a shelf life of 3 years. *Id.* at 38.

119. Due to the successful development of Nobelbar as a storage-stable phenobarbital sodium pharmaceutical product as discussed in PIF, a POSA would have been aware of the viability and effectiveness of phenobarbital sodium into a storage stable pharmaceutical product. Thus, a POSA would have been motivated, with a reasonable expectation of success, to produce such a storage-stable phenobarbital sodium composition. In view of the disclosures above, PIF teaches or makes the limitations of [1pre] obvious.

2. [1a] a single use dose vial, and

120. PIF describes Nobelbar as a lyophilized injection composed solely of the drug substance with no additives. Ex-1009 at 4, 7. The fact that Nobelbar contains no additives, including no antimicrobial preservatives, teaches a POSA that it is designed as a single-use vial, since multi-dose formulations ordinarily require preservatives to inhibit microbial growth after first use. *Id.* at 4, 7. Further, Nobelbar is indicated for neonatal convulsions (*Id.* at 1, 4, 13), a condition affecting a highly vulnerable population with limited immune defense. Given these patients' heightened susceptibility to infection, a POSA would be particularly motivated to avoid contamination, further reinforcing the rationale for a single-use dose.

121. PIF states that the reconstituted Nobelbar product should be used promptly—within 6 hours—and reports that related substances increase significantly (from 0.09% to 0.49%) within 24 hours after dissolution. Ex-1009 at 7, 8, 34. A POSA would understand that Nobelbar is intended for immediate, single-dose administration to ensure product quality and patient safety. Single-use packaging aligns with well-established industry practices, particularly in the context of parenteral products for vulnerable populations, where the stakes of contamination or impurity buildup are considerably higher.

122. Finally, PIF describes Nobelbar as containing “274 mg of phenobarbital sodium (250 mg as phenobarbital)” per vial. Ex-1009 at 1, 7. PIF

details that the approved dosage of Nobelbar for neonatal convulsions is an initial dose of 20 mg/kg administered intravenously. *Id.* at 13. For status epilepticus, Nobelbar may be administered to children or adults at a recommended dosage of 15-20 mg/kg per day. *Id.* at 13. These dosing regimens suggest that Nobelbar is provided in a single-use vial.

123. Thus, based on the no-additive composition, the absence of preservatives, the recommended immediate use after reconstitution, and the dosing regimens, a POSA would know that Nobelbar is formulated as a single-use vial and would be motivated, with a reasonable expectation of success, to adopt the same approach in developing other sterile, lyophilized phenobarbital sodium products. In view of the disclosures above, PIF discloses element [1a]. Even if Nobelbar was not formulated as a single-use vial, it would have been obvious and preferred for a POSA to use a single-use vial for the same reasons stated above.

3. [1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

124. West-Ward discloses that phenobarbital sodium injection has been available in concentrations of 65 mg/mL and 130 mg/mL with a fill volume of 1 mL, providing effective dosage forms. Ex-1013. Parker discloses phenobarbital sodium concentrations of 15-200 mg/mL. Ex-1012 at Abstract, [0017], [0031]. PIF also mentions that 30 mg, 50 mg, 60 mg, or 130 mg per 1 mL phenobarbital

sodium injection products were sold in the U.S. Ex-1009 at 42. A POSA would appreciate that these disclosures collectively establish a range of known, clinically viable phenobarbital sodium concentrations. Selecting or modifying dosage amounts, such as those disclosed in PIF, West-Ward, and Parker, is a routine, predictable adaptation within the skill of the art to achieve well-established therapeutic outcomes. Based on West-Ward's disclosure, a POSA would have been motivated to develop additional dosage increments and would have naturally chosen 100 mg as the midpoint between these two disclosed doses. Because these dosages have been used in commercial products without any unexpected safety or efficacy issues, a POSA would have recognized that there is no inventive step in merely choosing among these known dosages or combining them with other well-known formulation techniques.

125. A POSA would have further understood that a vial containing 65 mg corresponds to a single-use dose for a neonate weighing approximately 3.25 kg (7 pounds), and 130 mg corresponds to a single-use dose for an infant weighing around 6.5 kg (14 pounds). Such precise unit-dose packaging is particularly important in pediatric populations, where accurate dosing is critical. Consequently, a POSA would have been motivated, with a reasonable expectation of success, to use these well-accepted dosages, aware that they minimize formulation challenges and align with established dosing guidelines for phenobarbital sodium injections.

126. As such, a POSA would have a reasonable expectation of success in tailoring the amount of phenobarbital sodium to meet specific therapeutic needs, such as 65 mg, 100 mg, 130 mg, or 200 mg. This routine dosage selection process requires no inventive leap, as it simply leverages known concentrations and single-use vial sizes to accommodate different patient populations, including neonates and adults.

4. [1c] wherein the composition is sterile and lyophilized, and

127. PIF discloses Nobelbar, a lyophilized phenobarbital sodium formulation containing “274 mg of phenobarbital sodium (250 mg as phenobarbital)” per vial. Ex-1009 at 1, 7. Nobelbar is described as a lyophilized injection composed solely of the drug substance, with no additives. *Id.* at 4, 7, 13. Its approval for intravenous administration, particularly in neonates, teaches a POSA that it meets the rigorous safety standards governing such products and is the subject of robust sterility measures. *Id.* at 4, 13.

128. PIF also discloses that Nobelbar’s stability was tested under various physicochemical properties including pH, solubility, related substances, moisture content, loss on drying, endotoxin, formulation uniformity (mass deviation), foreign insoluble matter, insoluble particulates, and sterility. *Id.* at 6-7. PIF reports no changes in these test parameters under any storage conditions other than moisture content of the formulations. *Id.* These findings confirm that the Nobelbar

product remains stable and meets pharmacopeial standards for sterility and particulate matter even under accelerated storage conditions.

129. A POSA would have been aware from PIF that Nobelbar, a commercially available shelf-stable phenobarbital sodium freeze-dried product, is sterile. Indeed, a POSA would understand that any lyophilized phenobarbital sodium product must meet strict safety and regulatory requirements, including sterility, impurity content, and long-term stability, especially a product intended for neonatal use. Regulatory authorities mandate these requirements for injectable products to ensure patient safety and therapeutic efficacy. Moreover, as Nobelbar is lyophilized and intended for parenteral administration, a POSA would know that its production involves sterile filtration and aseptic processing, ensuring the final product's sterility.

130. Based on the successful development of Nobelbar as a lyophilized phenobarbital sodium product, a POSA would have recognized the viability and effectiveness of lyophilizing phenobarbital sodium. Furthermore, the test results relating to Nobelbar reported in PIF—which demonstrate no significant changes in purity or stability parameters—reinforce the feasibility of producing a sterile, particle-free, and shelf-stable phenobarbital sodium formulation. Thus, a POSA would have been motivated, with a reasonable expectation of success, to create such a sterile, lyophilized phenobarbital sodium composition.

5. [1d] wherein the composition comprises no less than 98% phenobarbital sodium.

131. PIF describes Nobelbar as a lyophilized injection composed solely of the drug substance, with no additives. Ex-1009 at 4, 7. This type of composition inherently indicates high drug content, as the absence of excipients or preservatives often ensures that the API constitutes or approaches at least 98% of the overall formulation. A POSA would reduce or eliminate additives as one of recognized strategies to keep the formulation simple and safe.

132. A POSA would also recognize that meeting or exceeding 98% phenobarbital sodium purity is particularly desirable for intravenous administration to neonates, given their heightened sensitivity to impurities. Ensuring high-purity compositions aligns with stringent safety standards and helps minimize the risk of adverse reactions, making it a natural goal for drug developers.

133. The practicality, stability, and safety of compositions disclosed in PIF exemplify the benefits of such high-purity formulations, motivating a POSA to pursue this approach with a reasonable expectation of success. Given Nobelbar's documented shelf life, impurity profile, and demonstrated efficacy, as disclosed in PIF, a POSA would have seen clear advantages in formulating a lyophilized phenobarbital sodium product composed of no less than 98% phenobarbital sodium, thereby mitigating potential degradation pathways and impurity accumulation. A POSA would, as a matter of routine, know how to modulate

secondary drying parameters to reduce residual moisture and solvent content such that the final composition would be at least 98% phenobarbital sodium.

134. For these reasons, claim 1 is obvious over PIF and West-Ward.

F. Obviousness of Claim 2 — Element by Element Claim Analysis

1. [2pre] The pharmaceutical product of claim 1,

135. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. [2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

136. PIF discloses that phenobarbital sodium is “extremely soluble in water” and “hygroscopic,” gradually decomposing when exposed to moist air. Ex-1009 at 7. A POSA would recognize that hygroscopic substances readily absorb moisture from the atmosphere, thereby increasing the potential for degradation and impurity formation.

137. Parker explains that the presence of hydroxyl ions from water in phenobarbital sodium formulations “results in a hydrolysis pathway that can destroy the phenobarbital ring complex,” generating “harmful” degradation byproducts such as PEAU, 2EPMM, and PBG. Ex-1012 at [0004], [0006], [0007], Table 1; *see also id.* at [0017], [0030], [0036], [0039], cl. 1. Furthermore, Parker

discloses that the degradation byproducts can also result from other conditions, such as “reactions with base, oxidation or subjecting the compound to heat.” *Id.* at [0007]. PIF also discloses that PEAU is one of the analogues that may be generated in the formulation manufacturing process. Ex-1009 at 12. A POSA would thus appreciate the critical importance of minimizing contact with water and other reactive agents to preserve phenobarbital sodium’s chemical stability.

138. Parker provides phenobarbital sodium solutions for injection that “do not generate any significant amounts of impurities during extended storage.” Ex-1012 at Abstract, [0017]. These solutions contain 15 to 200 mg/mL phenobarbital sodium, combined with a C1-C4 alcohol (e.g., ethanol) and a glycol, and are adjusted to a pH between 9 and 12 (preferably 9.2 to 10.2). *Id.* at Abstract, [0017], [0034], [0036], [0039], cls. 1-4. Parker further discloses container volumes ranging from about 0.5 to about 20 mL. *Id.* at [0058], cl. 10. By maintaining “no more than 50 mg/mL water,” Parker’s formulations significantly reduce hydrolysis-driven degradation. *Id.* at Abstract, [0017]. Indeed, Parker reports stable solutions with “no more than 0.8% PEAU impurity” after two years of room-temperature storage and no detectable phenyl butyric acid (PBA). *Id.* at [0017], cls. 1, 6.

139. A POSA would seek to control impurities by minimizing water and other reactive substances to ensure stability and safety, especially in injectable formulations where purity is paramount. Hydrolysis-induced degradation can lead

to the formation of potentially toxic byproducts, making low water content a key strategy for maintaining product quality.

140. PIF details the stability testing of Nobelbar under different conditions and evaluating different physicochemical properties, including pH, solubility, related substances, moisture content, loss on drying, endotoxin, foreign insoluble matter, insoluble particulates, and sterility. Ex-1009 at 6-8. These tests revealed “no changes” in any parameter apart from moisture content under both long-term (25 ± 2 °C / $60 \pm 5\%$ RH for 36 months) and accelerated (40 ± 2 °C / $75 \pm 5\%$ RH for 6 months) conditions. *Id.* PIF reports that the increase in the moisture content was thought to originate from the rubber stopper of the vial. *Id.* at 7. A POSA would conclude that minimizing moisture—via lyophilization—strongly yields stable phenobarbital sodium preparations.

141. Given the well-documented propensity of phenobarbital sodium to form impurities like PEAU, 2EPMM, and PBG when exposed to residual moisture, a POSA would be motivated to limit water in the formulation and packaging. Even minimal amounts of these impurities pose safety risks, especially in injectable phenobarbital sodium products. Therefore, a POSA would naturally rely on lyophilization to keep moisture content low, employ standard testing at room temperature (25 ± 2 °C) and under accelerated conditions (40 ± 2 °C), and

reconstitute the lyophilized product with 10 mL of aqueous solution for routine stability evaluations.

142. Indeed, the documented success of Nobelbar (as disclosed in PIF) would confirm that a storage-stable, amorphous phenobarbital sodium formulation can be achieved. A POSA would be motivated to produce such a product that, upon reconstitution and after six months at 40 °C, contains low levels of PEAU and certainly no more than 0.1%. By following the teachings of PIF and Parker, the POSA would have a reasonable expectation of success in creating these stable, lyophilized phenobarbital sodium compositions. Consequently, in view of the disclosures above, PIF, in view of Parker, meets element [2a], and renders claim 2 obvious.

G. Obviousness of Claim 3 — Element by Element Claim Analysis

1. [3pre] The pharmaceutical product of claim 1,

143. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. [3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.

144. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

H. Obviousness of Claim 4 — Element by Element Claim Analysis

1. [4pre] The pharmaceutical product of claim 1,

145. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. [4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

146. As described in connection with Element [2a], a POSA would recognize that phenobarbital sodium can also degrade into toxic impurities such as 2EPMM and PBG. *See supra* Section IX.F. As detailed above, minimizing water content through lyophilization and controlling storage conditions are well-known and important strategies for preventing hydrolysis and limiting the formation of these toxic byproducts. *See id.* A POSA would therefore apply the same approach—namely, rigorous drying to minimize the water content, and appropriate stability testing at 40 °C for six months—to ensure that, upon reconstitution in 10

mL of an aqueous solution, the composition contains no more than 0.05% of 2EPMM or PBG. *See id.*

147. By following the teachings of both PIF (regarding lyophilization and long-term stability) and Parker (on identifying and reducing phenobarbital sodium degradants), a POSA would have a reasonable expectation of success in achieving these impurity limits.

I. Obviousness of Claim 5 — Element by Element Claim Analysis

1. [5pre] The pharmaceutical product of claim 1,

148. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. [5a] wherein the composition is amorphous.

149. PIF discloses Nobelbar, a lyophilized phenobarbital sodium formulation containing “274 mg of phenobarbital sodium (250 mg as phenobarbital)” per vial. Ex-1009 at 1, 7, 13. Nobelbar is described as a freeze-dried injection composed solely of phenobarbital sodium, with no additives. *Id.* at 4, 7. PIF teaches that Nobelbar became Japan’s first intravenous phenobarbital preparation approved for neonatal convulsions and status epilepticus in October 2008. *Id.* at 4. A POSA would recognize that lyophilization is used to convert crystalline materials into amorphous forms. This transformation can be particularly beneficial for enhancing the solubility and dissolution rate of the API.

150. A POSA would seek an amorphous phenobarbital sodium product specifically because amorphous forms reconstitute more quickly than their crystalline counterparts. This is an obvious and important advantage in emergency or acute care settings, such as the treatment of neonatal convulsions, where timely administration can be life-saving. The ability to dissolve and administer the drug rapidly is especially valuable for neonates or infants experiencing seizures, where any delay in therapy is undesirable.

151. Given the documented success of stable formulations like Nobelbar as disclosed in PIF, a POSA would conclude, absent evidence to the contrary, that a lyophilized phenobarbital sodium composition would be amorphous and retain both high purity and stability over its shelf life. Thus, armed with PIF's disclosure and standard industry know-how, a POSA would be motivated to develop a stable and effective lyophilized amorphous phenobarbital sodium formulation, accomplishing long-term storage and rapid reconstitution. The formulation is designed for treating serious conditions such as neonatal seizures.

J. Obviousness of Claim 6 — Element by Element Claim Analysis

1. [6pre] The pharmaceutical product of claim 1,

152. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. **[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).**

153. As described in connection with Element [2a], a POSA would recognize the importance of controlling PEAU, one of the primary degradation products resulting from the hydrolysis of phenobarbital sodium. *See supra* Section IX.F. As detailed above, by employing the same strategies—lyophilization to minimize residual moisture and conducting stability testing under standard conditions—a POSA would confidently ensure the composition maintains minimal PEAU levels over extended storage. *Id.*

154. Additionally, because Nobelbar reportedly has a three-year shelf life, a POSA would understand that it exhibited stability for at least that duration. Ex-1009 at 38. Such testing intervals and conditions are standard industry practices to establish product robustness, impurity profiles, and overall stability, ensuring the final formulation meets stringent regulatory criteria. In this context, a POSA would be motivated to apply these techniques so that after 24 months at room temperature, upon reconstitution in 10 mL of an aqueous solution, the resulting composition would contain no more than 0.1% PEAU.

155. In view of both PIF's disclosure of a stable lyophilized phenobarbital sodium product and Parker's guidance on preventing hydrolytic degradants, a

POSA would have a reasonable expectation of success in maintaining low PEAU levels over this 24-month period. Accordingly, the POSA would be driven to produce such a composition, confident that it would satisfy the impurity requirement of at most 0.1% PEAU upon reconstitution for injection with 10 mL of an aqueous solution after stored at room temperature for 24 months.

K. Obviousness of Claim 7 — Element by Element Claim Analysis

1. [7pre] A pharmaceutical product, comprising:

156. As I understand from Petitioner’s counsel and as detailed in **Appendix B**, the preamble generally does not constitute a limitation and therefore does not limit the claims.

157. PIF discloses and renders obvious this element for the reasons set forth with respect to Element [1pre] in Ground 1. *See supra* Section IX.E.1.

2. [7a] a single use dose vial, and

158. PIF discloses and renders obvious this element for the reasons set forth with respect to Element [1a] in Ground 1. *See supra* Section IX.E.2.

3. [7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

159. PIF, Parker, and West-Ward disclose and render obvious this element for the reasons set forth with respect to Element [1b] in Ground 1. *See supra* Section IX.E.3.

4. [7c] wherein the composition is sterile and lyophilized,

160. PIF discloses and renders obvious this element for the reasons set forth with respect to Element [1c] in Ground 1. *See supra* Section IX.E.4.

5. [7d] wherein the composition comprises no less than 98% phenobarbital sodium, and

161. PIF discloses and renders obvious this element for the reasons set forth with respect to Element [1d] in Ground 1. *See supra* Section IX.E.5.

6. [7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).

162. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

L. Obviousness of Claim 8 — Element by Element Claim Analysis

1. [8pre] The pharmaceutical product of claim 7,

163. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section IX.K.

2. **[8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.**

164. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

M. Obviousness of Claim 9 — Element by Element Claim Analysis

1. **[9pre] The pharmaceutical product of claim 7,**

165. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section IX.K.

2. **[9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).**

166. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

N. Obviousness of Claim 10 — Element by Element Claim Analysis

1. **[10pre] The pharmaceutical product of claim 7,**

167. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section IX.K.

2. **[10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).**

168. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

O. Obviousness of Claim 11 — Element by Element Claim Analysis

1. **[11pre] The pharmaceutical product of claim 10,**

169. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [10pre]-[10a]. *Supra* Section IX.N.

2. **[11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).**

170. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

P. Obviousness of Claim 12 — Element by Element Claim Analysis

1. [12pre] The pharmaceutical product of claim 7,

171. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section IX.K.

2. [12a] wherein the composition is amorphous.

172. PIF discloses this element for the reasons set forth with respect to Element [5a] in Ground 1. *See supra* Sections IX.I.2.

Q. Obviousness of Claim 13 — Element by Element Claim Analysis

1. [13pre] The pharmaceutical product of claim 12,

173. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [12pre]-[12a]. *Supra* Section IX.P.

2. [13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

174. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See infra* Section IX.R.2.

R. Obviousness of Claim 14 — Element by Element Claim Analysis

1. [14pre] The pharmaceutical product of claim 1,

175. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. **[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).**

176. As described in Elements [2a] and [14a], a POSA would recognize that phenobarbital sodium can degrade into several toxic impurities, including PEAU, 2EPMM, and PBG. *See supra* Sections IX.F, IX.H. As detailed above, minimizing water content through lyophilization and controlling storage conditions are essential strategies for preventing hydrolysis and limiting the formation of these toxic decomposition products where even trace levels of harmful byproducts could cause significant risk with respect to patient safety. *See id.* A POSA would therefore continue to apply the same approach—controlling residual water content and conducting stability testing at room temperature for six months—to ensure that, upon reconstitution in 10 mL of an aqueous solution, the resulting composition contains no more than 0.05% PEAU, 2EPMM, or PBG. *See id.*

177. Because six months of storage under defined conditions, including room temperature, is a commonly used time interval in the pharmaceutical industry, a POSA would routinely employ such testing to confirm the formulation's stability and impurity profile. These well-known practices are important for showing that even after prolonged storage, the reconstituted composition meets

regulatory criteria for drug purity. By following the methods taught in PIF (which demonstrates a stable, lyophilized phenobarbital sodium product) and Parker (which details strategies for identifying and mitigating hydrolytic degradants), a POSA would be confident of maintaining very low levels of PEAU, 2EPMM, and PBG.

178. Accordingly, a POSA would have a reasonable expectation of success in achieving a lyophilized phenobarbital sodium composition that, after six months at room temperature, reconstitutes to contain no more than 0.05% PEAU and no more than 0.05% each of 2EPMM or PBG.

S. Obviousness of Claim 15 — Element by Element Claim Analysis

1. [15pre] The pharmaceutical product of claim 14,

179. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [14pre]-[14a]. *Supra* Section IX.R.

2. [15a] wherein the composition is amorphous.

180. PIF discloses this element for the reasons set forth with respect to Element [5a] in Ground 1. *See supra* Sections IX.I.2.

T. Obviousness of Claim 16 — Element by Element Claim Analysis

1. [16pre] The pharmaceutical product of claim 1,

181. PIF and West-Ward disclose and render obvious the limitations of [1pre]-[1d]. *Supra* Section IX.E.

2. [16a] wherein the product comprises the 100 mg dose in the single use dose vial.

182. As detailed in connection with Elements [1a] and [1b], a POSA would recognize that phenobarbital sodium doses of 65 mg, 100 mg, 130 mg, or 200 mg all fall within known, clinically acceptable ranges. *See supra* Sections IX.E.2-3. In particular, West-Ward and Parker establish a broad range of known concentrations up to 200 mg/mL, while PIF confirms U.S. market availability of phenobarbital sodium products in dosages such as 30 mg, 50 mg, 60 mg, and 130 mg per mL. Ex-1013; Ex-1012 at Abstract, [0017], [0031]; Ex-1009 at 42.

183. A 100 mg dose is a predictable and routine adaptation within the skill of the art to accommodate different patient populations and dosing regimens. *See supra* Section IX.E.3. As detailed in Element [1a], single-use vials ensure sterility and minimize contamination risks, particularly in vulnerable groups such as neonates. *See supra* Section IX.E.2. The 100 mg dosage can thus be tailored to meet therapeutic needs while maintaining the advantages of single-use packaging. A POSA would recognize no inventive step in selecting the 100 mg dose within the established range, relying on well-known formulation and dosing practices to provide both efficacy and safety.

184. Accordingly, in light of the disclosures in West-Ward, Parker, and PIF, a POSA would have a reasonable expectation of success in placing the 100 mg dose into a single-use vial.

U. Obviousness of Claim 17 — Element by Element Claim Analysis

1. [17pre] The pharmaceutical product of claim 7,

185. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section IX.K.

2. [17a] wherein the product comprises the 100 mg dose in the single use dose vial.

186. PIF, Parker, and West-Ward disclose and render obvious this element for the reasons set forth with respect to Element [16a] in Ground 1. *See supra* Section IX.T.2.

V. Obviousness of Claim 18 — Element by Element Claim Analysis

1. [18pre] The pharmaceutical product of claim 8,

187. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section IX.L.

2. [18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

188. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See supra* Section IX.R.2.

W. Obviousness of Claim 19 — Element by Element Claim Analysis

1. [19pre] The pharmaceutical product of claim 8,

189. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section IX.L.

2. [19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

190. PIF and Parker disclose and render obvious this element for the reasons set forth with respect to Element [14a] in Ground 1. *See supra* Section IX.R.2.

X. Obviousness of Claim 20 — Element by Element Claim Analysis

1. [20pre] The pharmaceutical product of claim 8,

191. PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section IX.L.

2. [20a] wherein the composition is amorphous.

192. PIF discloses this element for the reasons set forth with respect to Element [5a] in Ground 1. *See supra* Sections IX.I.2.

X. INVALIDITY GROUND 2: THE CHALLENGED CLAIMS ARE ANTICIPATED BY THE '608 PUBLICATION

193. The Original Applications lack written description for the full scope of the challenged claims. Consequently, the challenged claims are not entitled to a priority date earlier than June 30, 2022, the filing date of the '914 CIP application.

194. The '608 Publication was published on March 25, 2021, more than one year prior to June 30, 2022. Ex-1005 at cover. As I understand from Petitioner's counsel, the '608 Publication qualifies as § 102(a) prior art. In my opinion, the '608 Publication discloses every element of the challenged claims, either expressly or inherently.

195. The challenged claims are divided into limitations as shown in **Appendix C**.

A. The '076 Patent is Not Entitled to a Priority Date Earlier Than June 30, 2022

196. The legal principles relevant to priority and written description, as provided to me by Petitioner's counsel, are outlined in **Appendix B**. These legal standards were considered in forming the opinions expressed in this declaration.

197. I was asked to review the specifications of the '076 Patent, the specifications of the '914 CIP application, and the Original Applications to determine whether the Original Applications disclose the full scope of the challenged claims.

198. The Original Applications do not teach any compositions that contain organic solvents nor did they teach compositions that include crystalline phenobarbital sodium. Such compositions were disclosed for the first time in the '914 CIP application, filed on June 30, 2022. There are no Examples, Figures, Tables, or other guidance in the Original Applications to reasonably convey to a POSA that the inventors possessed or created any compositions that contain organic solvents or crystalline phenobarbital sodium.

1. Scope of the Challenged Claims

199. The challenged claims of the '076 Patent based on their plain language encompass lyophilized phenobarbital sodium compositions and products that contain organic solvents. Ex-1001 at cls. 1-20; *see also supra* Section VI.A. The challenged claims do not expressly exclude the inclusion of organic solvents. *See id.*

200. Certain challenged claims of the '076 Patent also encompass compositions containing crystalline phenobarbital sodium. Ex-1001 at cls. 1-4, 6-11, 13-14, and 16-19; *see also supra* Section VI.A. While dependent claims 5, 12, 15, and 20 specify that the phenobarbital sodium composition must be amorphous, claims 1-4, 6-11, 13-14, and 16-19 do not impose any such limitation. *Id.* at cls. 1-20. These broader claims allow the phenobarbital sodium compositions to exist in any form, including highly crystalline forms.

2. The Original Applications Lack Written Description for the Pharmaceutical Products of the Challenged Claims

201. The full scope of the challenged claims is not adequately taught or described in the Original Applications. Compositions containing organic solvents or crystalline phenobarbital sodium were disclosed for the first time in the '914 CIP application, filed on June 30, 2022.

202. As I understand from Petitioner's counsel and as detailed in **Appendix B**, the patent specification must provide sufficient written description for a POSA to reasonably conclude that the inventors possessed the full scope of the claimed subject matter as of the filing date. The Original Applications fail to disclose any lyophilized phenobarbital sodium pharmaceutical products containing organic solvents or lyophilized phenobarbital sodium compositions with crystalline forms, including highly crystalline, within the scope of the challenged claims, thereby not reasonably conveying to a POSA that the inventors possessed such compositions as of the dates of the Original Applications.

203. The '914 CIP application, filed on June 30, 2022, discloses for the first time that the inventors conducted "further experiments" to "investigate[] if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents." Ex-1007 at 61 (¶[00168]). The '914 CIP application further discloses that "the inventors tested isopropanol, tert-butanol, ethanol, and acetonitrile as co-

solvents,” with the concentration of the organic co-solvent being as high as 90%.

Id.

a. The Original Applications Do Not Disclose and Lack Written Description for Compositions and Pharmaceutical Products Containing an Organic Solvent

204. The Original Applications did not disclose the use of organic solvents. There are no Examples, Figures, Tables, or other disclosures in the Original Applications that describe, teach, or suggest any lyophilized phenobarbital sodium compositions or products containing organic solvents. *See generally* Ex-1003; Ex-1004. To the contrary, the Original Applications explicitly excluded organic solvents from the lyophilized amorphous phenobarbital sodium compositions described therein. Ex-1003 at 19 (¶[0078]) (“*The presently disclosed formulation does not contain any organic solvents or preservatives* which is specifically advantageous for administration to newborns and neonates.”) (emphasis added); Ex-1004 at 210 (¶[00101]) (same); Ex-1004 at 1213, pending cl. 28 (“wherein the phenobarbital sodium solution *does not contain an organic solvent*”) (emphasis added); Ex-1004 at 1215, pending cl. 43 (“wherein the sterile lyophilized amorphous phenobarbital sodium composition *does not contain an organic solvent*”) (emphasis added). The specifications emphasized this exclusion as a distinguishing feature, particularly for formulations intended for use in newborns and neonates. Ex-1003 at 19 (¶[0078]); Ex-1004 at 210 (¶[00101]) (same). A

POSA would have taken these statements in the Original Applications at face value and understood that the inventors' disclosed compositions must exclude organic solvents.

205. The term “organic solvent” appears only twice in the specifications of the Original Applications, both times requiring its exclusion. First, the specifications noted: “[i]n addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (*e.g.*, Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL), includes *organic solvents* such as alcohol, which are not desirable in general and indeed *not suitable for administration to newborns as described in the art.*” Ex-1003 at 7 (¶[0007]) (emphasis added); Ex-1004 at 195 (¶[0008]) (same). Second, the Original Applications stated: “[t]he presently disclosed formulation *does not contain any organic solvents* or preservatives which is specifically advantageous for administration to newborns and neonates.” Ex-1003 at 19 (¶[0078]) (emphasis added); Ex-1004 at 210 (¶[00101]) (same). These statements clearly distinguished the disclosed formulations from prior art phenobarbital sodium formulations by emphasizing that organic solvents are “*not desirable*” and “*not suitable for administration to newborns.*” Ex-1003 at 7 (¶[0007]) (emphasis added); Ex-1004 at 195 (¶[0008]) (same).

206. The claims of the '598 Patent, which issued from the Original Applications, are consistent with this exclusion. Ex-1006 at cls. 1-15. For instance, independent claim 1 of the '598 Patent requires that “the phenobarbital sodium solution does not contain an organic solvent.” *Id.* at cl. 1.

207. During the prosecution of the '881 application—which later issued as the '598 Patent—arguments against prior art rejections reinforced this exclusion. For example, the Patent Owner argued that the claimed phenobarbital sodium compositions “must be free of organic solvents,” distinguishing them from prior art such as Parker, which disclosed formulations containing organic solvents. Ex-1004 at 1216. This distinction was important, as the Examiner agreed “in view of the fact that Parker uses organic solvents which are excluded by the instant claims” and noted in the “Reasons for Allowance” that “[t]he prior art neither teaches, nor fairly suggests the instantly claimed method of making a lyophilized sodium phenobarbital. The closest prior art is that of Parker [], which includes *organic solvents which are excluded by the instantly claimed method*. The instantly claimed method is therefore allowable over the prior art of record.” Ex-1004 at 1241-42 (emphasis added). These statements demonstrate that the exclusion of organic solvents was central to the scope of the Original Applications and the allowed claims of the '598 Patent.

208. A lyophilized phenobarbital sodium composition containing organic solvents was disclosed for the first time in the '914 CIP application, filed on June 30, 2022. The specifications of the '914 CIP application describe how the inventors had to conduct “further experiments” to “investigate[] if stable lyophilized phenobarbital preparations could be prepared . . . using one or more water miscible co-solvents.” Ex-1007 at 61 (¶[00168]). These experiments included testing organic co-solvents such as isopropanol, tert-butanol, ethanol, and acetonitrile, with the concentration of the organic co-solvent reaching as high as 90%. *Id.* This disclosure represented a significant departure from the Original Applications, which explicitly excluded organic solvents.

209. Given the explicit exclusion of organic solvents in the Original Applications and their emphasis on the advantages of this exclusion for neonatal and newborn administration, the Original Applications do not reasonably convey to a POSA that the inventors possessed lyophilized phenobarbital sodium pharmaceutical compositions or products containing organic solvents until June 30, 2022, the filing date of the '914 CIP application.

b. The Original Applications Do Not Disclose and Lack Written Description for Compositions and Pharmaceutical Products Having Crystalline Phenobarbital Sodium

210. The Original Applications also lack written description for the full scope of claims 1-4, 6-11, 13-14, and 16-19 because they only disclose amorphous

formulations of lyophilized phenobarbital sodium. None of the examples, figures, or other disclosures in the Original Applications describe, teach, or suggest lyophilized phenobarbital sodium compositions in a *crystalline* form. *See generally* Ex-1003; Ex-1004. Instead, the disclosures repeatedly affirm that the alleged invention is limited to *amorphous* compositions:

- “A composition of, method for producing, and use of an *amorphous* lyophilized Phenobarbital Sodium having high purity are presented. The *amorphous* lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alphaphenylbutyrylguanidine (PBG)) upon reconstitution in water.” Ex-1003 at 34; Ex-1004 at 233 (emphasis added).
- “The contemplated composition is an *amorphous* lyophilized Phenobarbital Sodium with high stability and purity. . . . The *amorphous* composition is a storage-stable form of lyophilized Phenobarbital Sodium.” Ex-1003 at 8 (¶[0009]); Ex-1004 at 196 (¶[0010]) (emphasis added).
- “According to contemplated embodiments as disclosed herein, the *amorphous* lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT.” Ex-1003 at 9 (¶[0014]); Ex-1004 at 197 (¶[0017]) (emphasis added).
- “These methods include adding saline or dextrose to the lyophilized *amorphous* Phenobarbital Sodium powder as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual.” Ex-1003 at 10 (¶[0022]); Ex-1004 at 199 (¶[0025]) (emphasis added).

- “In other embodiments, the lyophilized *amorphous* Phenobarbital Sodium is a powder dose of 65 mg or 130 mg.” Ex-1003 at 10-11 (¶[0022]) (emphasis added).
- “Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the lyophilized *amorphous* Phenobarbital Sodium powder for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after lyophilization” Ex-1003 at 11 (¶[0023]) (emphasis added).
- “Therefore, the inventors also contemplate lyophilized *amorphous* Phenobarbital Sodium.” Ex-1003 at 11 (¶[0024]) (emphasis added).
- “In particular, with reference to the polarized light photomicrographs of **Figs. 1A-1F** and the XRPD analysis shown in **Fig 5A-5D**, the storage-stable lyophilized Phenobarbital Sodium powder has an *amorphous* structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an *amorphous* structure that contributes to the observed stability of this composition upon reconstitution in water.” Ex-1003 at 16 (¶[0070]); Ex-1004 at 205 (¶[0073]) (emphasis added).
- “With reference to **Figs. 5B-5C**, the lyophilized Phenobarbital Sodium is *amorphous*.” Ex-1003 at 19 (¶[0078]); Ex-1004 at 210 (¶[00101]) (emphasis added).
- “The lyophilized *amorphous* formulation that was produced resulted in surprising, unexpected and desirable results.” Ex-1004 at 196 (¶[0011]) (emphasis added).
- “In other embodiments, the *lyophilized amorphous* Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg.” Ex-1004 at 199 (¶[0025]) (emphasis added).

- “Another embodiment is directed to a pharmaceutical composition that consists of *lyophilized* amorphous Phenobarbital Sodium.” Ex-1004 at 207 (¶[0081]) (emphasis added).
- “The method includes adding saline or dextrose to a composition containing *lyophilized* amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual.” Ex-1004 at 209 (¶[0096]) (emphasis added).

211. All claims of the '598 Patent, which issued from the Original Applications, are consistent with these disclosures and are expressly limited to *amorphous* compositions. Ex-1006 at cls. 1-15. Each claim of the original claim set submitted to the Patent Office in connection with the Original Applications was limited to *amorphous* compositions, emphasizing that the inventors viewed their inventions as including only *amorphous* products. Ex-1004 at 230-32.

212. Although the term “crystalline” appears in the specifications of the Original Applications, it is only used to describe prior art or to contrast with the disclosed amorphous compositions:

- First, the Original Applications describe prior art liquid formulations containing “crystalline granules or crystals dissolved in an aqueous solvent.” Ex-1003 at 6 (¶[0004]); Ex-1004 at 194 (¶[0005]).
- Second, the Original Applications state that the disclosed amorphous compositions provide superior stability compared to conventional crystalline forms, stating that “[t]hese results are particularly surprising and unexpected in view of the fact that

- conventional wisdom teaches that crystalline material is more stable than amorphous material.” Ex-1004 at 196 (¶[0011]).
- Third, the Original Applications describe USP grade phenobarbital in the prior art as polymorphous, containing “both crystalline and non-crystalline material.” Ex-1003 at 17 (¶[0071]); Ex-1004 at 205-06 (¶[0074]).
- Finally, the Original Applications explicitly teach that “the lyophilized Phenobarbital Sodium [of the claimed invention] is *non-crystalline* unlike the USP grade P API.” Ex-1003 at 19 (¶[0078]) (emphasis added), 112 (Fig. 5D); Ex-1004 at 210 (¶[00101]), 272 (Fig. 5D).

In each instance, the term “crystalline” is used to describe the prior art or to contrast with the amorphous compositions disclosed in the Original Applications. The Original Applications consistently emphasize the non-crystalline nature of the disclosed compositions. *See* Ex-1003 at 19 (¶[0078]) (“the lyophilized Phenobarbital Sodium is non-crystalline” and “the lyophilized Phenobarbital Sodium is amorphous”); Ex-1004 at 210 (¶[00101]) (same).

213. The Original Applications disclose that “[p]referably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%,” and that alternately, it can be 100% amorphous. Ex-1004 at 196 (¶[0012]). Based on the Original Applications, the lyophilized phenobarbital sodium of the claimed invention was amorphous. Ex-1003 at 19 (¶[0078]), 112 (Fig. 5D); Ex-1004 at 210 (¶[00101]), 272 (Fig. 5D).

214. During prosecution of the Original Applications, the Patent Owner reaffirmed that their compositions were limited to amorphous forms, relying on the advantageous properties of non-crystalline phenobarbital sodium:

A skilled artisan in the art would appreciate that the amorphous form of Phenobarbital Sodium lacks ordered crystalline structure and tight packing, which would normally prevent or substantially reduce degradation processes. Amorphous forms do not provide such limitations and therefore would be normally considered as inferior to crystalline forms. Because of that general notion, the storage performance of the lyophilized amorphous form of Phenobarbital Sodium is surprising and unexpected.

Ex-1004 at 643 (Decl. of Dr. Dasaradhi Lakkaraju). The Patent Office agreed, noting that “crystalline form [of phenobarbital sodium] is not the claimed subject matter [of the ’881 application].” Ex-1004 at 658. The prosecution history of the ’881 application further underscores that the Original Applications disclose only amorphous formulations of lyophilized phenobarbital sodium.

215. A crystalline form of lyophilized phenobarbital sodium product was suggested for the first time by Patent Owner in the ’914 CIP application, filed on June 30, 2022. The specification of the ’914 CIP application describes how the inventors conducted “further experiments” to “investigate[] if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents.” Ex-

1007 at 61 ([00168]). This disclosure represented a significant departure from the Original Applications, which explicitly focused on amorphous forms.

216. By consistently emphasizing amorphous compositions in the Original Applications, the Patent Owner made clear that their invention in the Original Applications was limited to amorphous lyophilized compositions. The Original Applications do not reasonably convey to a POSA that the inventors possessed lyophilized phenobarbital sodium pharmaceutical compositions or products containing crystalline forms until June 30, 2022, the filing date of the '914 CIP application.

217. Consequently, the Original Applications neither teach compositions containing organic solvents nor crystalline phenobarbital sodium, with such compositions first disclosed in the '914 CIP application filed on June 30, 2022, rendering the challenged claims not entitled to a priority date of the filing dates of the Original Applications.

B. Overview of the '608 Publication

218. The '608 Publication, titled "Lyophilized compositions of phenobarbital sodium salt," was published on March 25, 2021. Ex-1005 at cover. The '608 Publication discloses "compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water." *Id.* at [0002]. It describes phenobarbital with an

IUPAC name of “sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate,” a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$. *Id.* at [0072].

219. In the Background section, the '608 Publication highlights issues associated with the use of phenobarbital sodium in the prior art, noting its use as a barbiturate for treating seizures and its typical presentation as a liquid formulation for intramuscular or intravenous administration. *Id.* at [0005]. Prior art formulations, such as those described in Parker, used a C1–C4 alcohol and glycol solvent system but suffered from stability issues, as phenobarbital sodium readily hydrolyzes in water to form toxic degradation products, including “phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG).” *Id.* at [0005]-[0006]. The '608 Publication describes previous efforts to minimize such degradants, but impurities like PEAU remained present in undesirable amounts after extended storage in Parker’s liquid formulation. *Id.* at [0007].

220. The '608 Publication describes its invention as “amorphous lyophilized Phenobarbital Sodium with high stability and purity,” with a purity level of no less than 98%. *Id.* at [0010], [0104]. It discloses that the compositions produce fewer toxic degradation impurities and offers superior stability compared to phenobarbital sodium products in existence at the time. *Id.* at [0011].

221. The '608 Publication also states that the percentage of the lyophilized formulation that is amorphous is “preferably . . . at least 20%,” with possible ranges up to 100%. *Id.* at [0012]. Additionally, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012], [0106].

222. The '608 Publication indicates that typical embodiments of its invention include powder doses of 65 mg, 100 mg, 130 mg, and 200 mg, which are intended for intramuscular or intravenous injection. *Id.* at [0025], [0099].

223. The '608 Publication discloses preparing the storage-stable form of phenobarbital sodium by dissolving phenobarbital sodium in water to form a solution with a pH between 9.2 and 10.2, then lyophilizing the bulk solution. *Id.* at [0013], [0075], [0077]. To adjust the pH, hydrochloric acid (HCl) or sodium hydroxide (NaOH) is used. *Id.* at [0015], [0077]. Preferred embodiments include sparging water for injection (WFI) with nitrogen and cooling it to 2-8°C before dissolving phenobarbital sodium. *Id.* at [0014], [0075]. The solution is also filtered before lyophilization. *Id.* at [0018], [0078].

224. The '608 Publication further discloses that the reconstituted lyophilized phenobarbital sodium can be used with WFI, 0.9% saline, or 5% dextrose for IV or IM administration. *Id.* at [0101], [0119]. Post-reconstitution, the solution contains no more than 0.2% PEAU, 2EPMM, or PBG, and preferably

0.05% or less PEAU with no detectable amounts of the other impurities. *Id.* at [0024]. The publication notes that the lyophilized composition forms no significant amounts of toxic degradation products after up to six months of storage under room temperature (RT) or accelerated conditions (40°C.), which is equivalent to 24 months at room temperature. *Id.* at [0016]-[0017], [0071], [0073], [0088]-[0091].

225. The '608 Publication also discloses that lyophilization can be performed by aliquoting phenobarbital sodium into sterile, single-use dose vials, with doses such as 65 mg and 130 mg, for subsequent lyophilization. *Id.* at [0079].

226. Tables 2 and 3 of the '608 Publication compare the stability of the disclosed 65 mg and 130 mg lyophilized phenobarbital sodium formulations with marketed liquid phenobarbital sodium for injection USP (Westward Pharmaceuticals), showing superior stability even after 15 months:

TABLE 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder											
Product Name											
Phenobarbital Sodium for Injection USP, 65 mg/mL (Marketed product)						Phenobarbital Sodium for Injection USP, 65 mg/Vial (Nivagen formulation- NPH1907)					
Formulation Type											
Liquid						Lyophilized powder					
Stability Data											
Test	Initial	3 Months		6 Months		3 Months		6 Months		15 Months	
		RT	ACC	RT	ACC	RT	ACC	RT	ACC	RT**	
		25° C.,	40° C.,	25° C.,	40° C.,	25° C.,	40° C.,	25° C.,	40° C.,	25° C.,	
		60%	75%	60%	75%	60%	75%	60%	75%	60%	
		RH	RH	RH	RH	RH	RH	RH	RH	RH	
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
after reconstitution											
Identification	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
pH*	9.3	9.8	9.7	9.6	9.6	9.8	9.6	9.6	9.7	9.7	9.8
% Assay of Phenobarbital Sodium	102.4	97.6	103.1	96.3	86.7	99.1	98.7	97.4	100.0	99.3	96.0
% degradation (Area percent)	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
2EPMM											
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	0.5	1.0	3.7	1.4	5.8	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	BQL	BQL	0.1	BQL	0.3	BQL	BQL	BQL	0.07	0.06	0.04
Total degradation products	0.5	1.0	3.8	1.4	6.1	BQL	BQL	BQL	0.07	0.06	0.04

CCVS: Clear Colorless Viscous Solution;

CCS: Clear Colorless Solution;

WLP: White Lyophilized powder

\$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.

BQL: Below Quantitation Limit; (QL=0.05%);

ND: Not Detected

2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;

PBG: α -phenylbutyrylguanidine,

PEAU: phenylethylacetylurea or Pheneturide

*pH of both liquid and lyophilized formulations are measured at 65 mg/mL concentration

**The samples were stored at 30 $\pm$ 2° C., 65% RH $\pm$ 5

TABLE 3

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation											
Product Name											
Phenobarbital Sodium for Injection USP, 130 mg/mL (Marketed product)						Phenobarbital Sodium for Injection USP, 130 mg/vial (Nivagen formulation-NPH1912)					
Formulation Type											
Liquid						Lyophilized powder					
Stability Data											
Test	Initial	3 Months		6 Months		Initial	3 Months		6 Months		15 Months
		RT	ACC	RT	ACC		RT	ACC	RT	ACC	
		25° C.,	40° C.,	25° C.,	40° C.,		25° C.,	40° C.,	25° C.,	40° C.,	
		60% RH	75% RH	60% RH	75% RH		60% RH	75% RH	60% RH	75% RH	
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
Identification	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
pH*	9.5	9.9	9.9	9.8	9.7	9.8	9.8	9.8	9.8	9.8	10.0
% Assay of Phenobarbital Sodium	100.8	95.5	92.9	95.2	90.9	98.3	100.1	97.9	100.2	99.4	98.3
Related Substances (% Area)	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
2EPM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PBG	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL
PEAU	0.5	0.9	2.8	1.1	4.3	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	ND	BQL	0.1	BQL	0.4	BQL	BQL	BQL	0.05	0.05	0.04
Total degradation products	0.5	0.9	2.9	1.1	4.7	BQL	BQL	BQL	0.05	0.05	0.04

CCVS: Clear Colorless Viscous Solution;

CCS: Clear Colorless Solution;

WLP: White Lyophilized powder

\$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.

BQL: Below Quantitation Limit; (QL=0.05%);

ND: Not Detected

2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;

PBG: α -phenylbutyrylguanidine,

PEAU: phenylethylacetylurea or Pheneturide

*pH for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution

**The samples were stored at 30 $\pm$ 2° C., 65% RH $\pm$ 5

Id. at Tables 2 and 3, cols. 7-8.

227. Additional stability data is provided for phenobarbital sodium formulations across various doses (65 mg, 100 mg, 130 mg, and 200 mg), showing room temperature and accelerated stability conditions of 25°C/65% RH and 40°C/75% RH, respectively:

TABLE 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	Spec.	Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
		Jun. 5, 2020	2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.7	9.8
% Assay	90.0-105.0	100.1	100.1	100.1
Phenobarbital Sodium				
Related Substances (% Area)	NMT 0.2%	BQL	ND	ND
2EPM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.24
Total degradation products	NMT 1.5%	BQL	0.09	0.27
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

TABLE 7-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	Spec.	Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
		Jun. 5, 2020	2-8° C.	RT
Note Book Reference		192045-163 to 189	192045-163-183	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B) Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial (Reconstitution in 10 mL Water)				
Test	Specification	Reconstituted Solution Stability after 20 hrs		
		Initial	2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay	90.0-105.0	103.3	103.4	102.8
Phenobarbital Sodium				
Related Substances (% Area)	NMT 0.2%	BQL	ND	BQL
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified	NMT 0.2%	BQL	0.06	0.27

TABLE 8-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B) Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial (Reconstitution in 10 mL Water)				
Test	Specification	Reconstituted Solution Stability after 20 hrs		
		Initial	2-8° C.	RT
degradation product				
Total degradation products	NMT 1.5%	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 9

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)								
Tests	Specifications	Shelf life	Time					
			2 hrs		4 hrs		24 hrs	
		Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.2-10.2	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	90.0%-105.0%	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL
2EPMM								
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL

TABLE 9-continued

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)								
Tests	Specifications	Shelf life	Time					
			2 hrs		4 hrs		24 hrs	
		Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Any unspecified degradation product @ RRT 0.37	NMT 0.2%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	NMT 1.5%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	To be reported	158	NP	NP	NP	NP	159	158

CCS: Clear colourless solution;
ND: Not detected;
BQL: Below Quantitation limit,
NP: Not performed;
2EPMM: 2-ethylphenylmalonamide monohydrate;
PBG: Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

Declaration of Dr. Suryanarayanan for *Inter Partes* Review of U.S. Patent No. 11,878,076

TABLE 10

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch#NPH2020 Fill Volume: 1.05 mL	Date Manufactured: Jan. 20, 2020
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);		Date Initiated: Feb. 14, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV; Siegfried USA, LLC Lot#1845X007; Re-test Date: Nov. 16, 2023		
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6730GC 6 TP3)		
Configuration	Inverted	Stability	Flip Off Seals: Wheaton, 13 mm Red Plastic top flip off with Aluminum Seal, Lot#224202 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

Test	Spec.	Initial DOA:	1 Month DOA: Mar. 29, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020	
		Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.5	9.5
% Assay	90.0%-105.0%	98.6	301.6	101.5	101.3	100.5	100.0	101.2
Phenobarbital Sodium Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL

TABLE 10-continued

Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.3	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192046-23 to 45		192045-135 to 153		192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

Declaration of Dr. Suryanarayanan for *Inter Partes* Review of U.S. Patent No. 11,878,076

TABLE 11

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch#NPH2020	Date Manufactured:
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);	Fill Volume: 1.05 mL	Jan. 20, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV; Siegfried USA, LLC Lot#1845X007; Re-test Date: Nov. 16, 2023		Date Initiated: Feb. 14, 2020
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6730GC 6 TP3)	Flip Off Seals: Wheaton, 13 mm Red Plastic top flip off with Aluminum Seal, Lot#224202	
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

Test	Spec.	Initial DOA: Feb. 18, 2020	1 Month DOA: Mar. 23, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020	
			RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.5	9.5
% Assay	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Phenobarbital Sodium Related Substances (% Area)	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
2EPMM								
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.3	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192045-23 to 45		192045-135 to 153		192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 12

Product	Phenobarbital Sodium for	Batch#NPH2031A	Date Manufactured:
Name	Injection USP, 200 mg/vial	Fill Volume: 2.1 mL	Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear		Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);		Jun. 9, 2020

TABLE 12-continued

API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV; Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024			
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper			
Configuration	Inverted	Stability	Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)	
Test	Spec.	Initial DOA: Jun. 5, 2020	3 Months DOA: Sep. 4, 2020	
			RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay	90.0-105.0	100.1	98.1	101.0
Phenobarbital Sodium				
Related Substances (% Area)	NMT 0.2%	ND	ND	ND
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.09	0.09
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetyleurea

TABLE 13

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial		Batch#NPH2031A	Date Manufactured: Jun. 3, 2020	
Vial	10 mL Tubular Serum Bottle Clear		Fill Volume: 2.1 mL	Date Initiated: Jun. 9, 2020	
Make	Wheaton, Part# 223586; Batch#5192875;		Jun. 9, 2020		
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV; Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024				
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203		
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)		
			Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC	
Description	WLP	WLP	WLP	WLP	
Appearance	CCS	CCS	CCS	CCS	
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	
% Assay	90.0-105.0	103.3	102.8	103.6	
Phenobarbital Sodium					
Related Substances (% Area)	NMT 0.2%	BQL	ND	ND	
2EPMM					

Declaration of Dr. Suryanarayanan for *Inter Partes* Review of U.S. Patent No. 11,878,076

TABLE 13-continued

PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.1	0.08
Water Content by Karl Fischer	NMT 3.0%	0.8	0.9	1.1
Note Book Reference		192045-163 to 189	192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 16

Product Name	Phenobarbital Sodium for Injection USP, 100 mg/vial	Batch#NPH1980				Date Manufactured: Sep. 25, 2019			
Vial Make	5 mL Clear Untreated Article#9621139054 5 mL Clear Treated Article#9621130486	Siegfried USA, LLC Lot#1845X006; Re-test Date: Nov. 16, 2023				Date Initiated: Sep. 30, 2019			
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;	Siegfried USA, LLC Lot#1845X006; Re-test Date: Nov. 16, 2023				Flip Off Seals: Wheaton, 13 mm			
Stopper Used	Aptar stelini 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper, Lot#G702/91884	Red Plastic top flip off with Aluminum Seal, Lot# NA				25° C., 60% RH (RT) & 40° C., 75% RH (ACC)			
Configuration	Inverted	Stability							

Test	Spec.	1 Month						3 Months				6 Months			
		Initial		RT		ACC		RT		ACC		RT		ACC	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.5	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay	90.0%-105.0%	98.4	97.8	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6
Phenobarbital Sodium															
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	ND	ND	ND	ND
2EPMM															
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

TABLE 16-continued

Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	1.0	1.1	1.3	1.2	1.1	1.6	1.5	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031-169 to 183		192039-44 to 52		192045-52 to 85							

WLP: White Lyophilized powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
UT: Untreated;
T: Treated;
ND: Not Detected;
NMT: Not More Than;
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α -Phenylbutyrylguanidine;

Id. at Tables 7-13⁸, 16; *see also id.* at [0103].

228. The '608 Publication further discloses specific lyophilization parameters used for these formulations, detailing the steps for achieving stable and highly pure products:

TABLE 15

Lyophilization Cycle parameters.									
		Lyophilization Cycle 1*				Lyophilization Cycle 2**			
Section	Phase	Condenser set point C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]	Condenser set point ° C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]
1	Loading		off	5	n.a.		off	-5	n.a.
2	Freezing		off	-5	5		off	-5	10
3	Freezing		off	-50	60		off	-52	120
(Ramp)									

TABLE 15-continued

Lyophilization Cycle parameters.									
		Lyophilization Cycle 1*				Lyophilization Cycle 2**			
Section	Phase	Condenser set point ° C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]	Condenser set point ° C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]
4	Freezing		off	-10	30		off	-52	180 (Hold)
5	Freezing	-50	off	-50	120		n.a.	n.a.	n.a.
6	Evacuation		75	-50	30	-60	50	-45	30
7	Primary drying		75	-50	400 (Hold)		50	-42	100 (Ramp)
8	Primary drying		75	-45	350 (Hold)		50	-42	1120 (Hold)
9	Primary drying		75	-43	300 (Hold)		n.a.	n.a.	n.a.
10	Primary drying		75	-35	250 (Hold)		n.a.	n.a.	n.a.
11	Primary drying		75	-20	60 (Hold)		n.a.	n.a.	n.a.
12	Primary drying		75	0	120 (Hold)		n.a.	n.a.	n.a.
13	secondary drying		75	50	120 (Hold)		50	35	100 (Ramp)
14	secondary drying		75	25	120 (Hold)		50	35	420 (Hold)

Lyophilization Cycle 1*: 65 mg/vial, 130 mg/vial and 100 mg/vial samples disclosed in Tables 1, 2, 3, 16 and 17

Lyophilization Cycle 2**: NPH2031A (200 mg/vial Phenobarbital Sodium) and NPH2031B (200 mg/vial in Phenobarbital Sodium and 90 mg/vial Sodium Chloride, NPH2020 (65 mg/vial) and NPH2021 (130 mg/vial)

⁸ The Patent Owner repeated the same six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (as shown in Table 10) for Table 11.

Id. at [0123], Table 15.

C. Anticipation of Claim 1 — Element by Element Claim Analysis

1. [1pre] A storage stable pharmaceutical product, comprising:

229. As I understand from Petitioner’s counsel and as detailed in

Appendix B, the preamble generally does not constitute a limitation and therefore does not limit the claims.

230. The ’608 Publication discloses “compositions of storage-stable lyophilized Phenobarbital Sodium” and “pharmaceutical product[s] including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration.” Ex-1005 at Abstract, [0002], [0026]; *see also id.* at [0009]-[0011], [0013], [0015]-[0020], [0023]-[0024], [0071], [0073]-[0075], [0081]-[0082], [0088]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 6-13, 16, cls. 1-2, 8-12. As the ’608 Publication describes the limitations, the ’608 Publication teaches limitations of [1pre].

2. [1a] a single use dose vial, and

231. The ’608 Publication teaches aliquoting phenobarbital sodium into “single use dose vials for lyophilization.” Ex-1005 at [0079] (“[T]o produce 65 mg or 130 mg doses of lyophilized Phenobarbital Sodium, a batch may be dissolved, mixed, pH adjusted if necessary, and filtered and then aliquoted into single use

dose vials for lyophilization.”); *see also id.* at cl. 15. The ’608 Publication teaches limitations of [1a].

3. [1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

232. The ’608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg. Ex-1005 at [0025] (disclosing 65 mg, 130 mg, 100 mg, and 200 mg powder doses); *see also id.* at [0008], [0068]-[0069], [0075], [0079], [0093], [0099], [0102]-[0103], [0105]-[0106], [0119]-[0124], Figs. 5B-5C, Tables 1-3, 6-17, cls. 13, 19. The ’608 Publication teaches limitations of [1b].

4. [1c] wherein the composition is sterile and lyophilized, and

233. The ’608 Publication teaches compositions of, methods of producing, and use of a lyophilized amorphous phenobarbital sodium formulation with high storage stability and purity. Ex-1005 at [0010], [0013]; *see also id.* at Abstract, [0002], [0011], [0015]-[0020], [0023], [0025]-[0027], [0071], [0073]-[0075], [0079]-[0082], [0088]-[0096], [0101]-[0108], [0120]-[0121], [0123]-[0124], Tables 1-3, 7-13, 15-17, cls. 1-2, 8-12, 16. The ’608 Publication further discloses filtering the phenobarbital sodium solution prior to lyophilization “to remove any foreign particles” and that phenobarbital sodium “solution may be aliquoted into sterile

containers.” *Id.* at [0018], [0078]-[0079], [0094]; *see also id.* at cls. 14-15.

The ’608 Publication teaches limitations of [1c].

5. [1d] wherein the composition comprises no less than 98% phenobarbital sodium.

234. The lyophilized phenobarbital sodium disclosed in the ’608 Publication contains “no less than 98% Phenobarbital Sodium” Ex-1005 at [0010], [0024], [0071], [0103]-[0104], [0120]-[0121], [0124], Table 2-3, 7-13, 16; *see also id.* at Abstract, [0002]. The ’608 Publication teaches limitations of [1d].

235. For these reasons, claim 1 is anticipated by the ’608 Publication.

D. Anticipation of Claim 2 — Element by Element Claim Analysis

1. [2pre] The pharmaceutical product of claim 1,

236. The ’608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [2pre].

Supra Section X.C.

2. [2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

237. The ’608 Publication discloses storage stable lyophilized compositions of phenobarbital sodium salt with high purity that are essentially void of impurities upon reconstitution in 10 mL of Water for Injection or 5% Dextrose.

Ex-1005 at Abstract, [0002], [0101], [0119]; *see also id.* at [0006]-[0007], [0009], [0025], [0071], [0096], [0106], cl. 16. The '608 Publication further discloses that the lyophilized phenobarbital sodium compositions “do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073]; *see also id.* at Abstract, [0006]-[0007], [0017], [0023]. Once the lyophilized phenobarbital sodium has been reconstituted after storage “for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC),” the '608 Publication discloses that the reconstituted solution forms “no more than 0.1% phenylethylacetylurea (PEAU).” *Id.* at [0016], [0088]; *see also id.* at [0013], [0024], [0071], [0082], [0089], [0091]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 7-13, 16, cls. 2, 8-9, 11-12. The '608 Publication notes that the accelerated stability conditions are 40° C, 75% relative humidity (“RH”). *Id.* at [0013], [0016], [0071], [0103], [0121], [0124], Tables 2-3, 10-13, 16. The '608 Publication teaches limitations of [2a].

E. Anticipation of Claim 3 — Element by Element Claim Analysis

1. [3pre] The pharmaceutical product of claim 1,

238. The '608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [3pre].

Supra Section X.C.

2. **[3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.**

239. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

F. Anticipation of Claim 4 — Element by Element Claim Analysis

1. **[4pre] The pharmaceutical product of claim 1,**

240. The '608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [4pre].

Supra Section X.C.

2. **[4a] wherein the composition has the property that when the composition is stored at 40°C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).**

241. The '608 Publication discloses storage stable lyophilized compositions of phenobarbital sodium salt with high purity that are essentially void of impurities upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1005 at Abstract, [0002], [0101], [0119]; *see also id.* at [0006]-[0007], [0009], [0025], [0071], [0096], [0106], cl. 16. The '608 Publication further discloses that the lyophilized phenobarbital sodium compositions “do[] not form significant (e.g.,

not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073]; *see also id.* at Abstract, [0006]-[0007], [0017], [0023]. The ’608 Publication further discloses that “the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions.” *Id.* at [0016]; *see also id.* at [0013], [0017], [0024], [0071], [0090]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 7-13, 16, cls. 10-12. As previously described in Element [2a], the ’608 Publication notes that the accelerated stability conditions are 40° C, 75% RH. *Id.* at [0013], [0016], [0071], [0103], [0121], [0124], Tables 2-3, 10-13, 16; *see supra* Section X.D.2. The ’608 Publication teaches the limitations of [4a].

G. Anticipation of Claim 5 — Element by Element Claim Analysis

1. [5pre] The pharmaceutical product of claim 1,

242. The ’608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [5pre]. *Supra* Section X.C.

2. [5a] wherein the composition is amorphous.

243. The '608 Publication discloses “[a] composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium.” Ex-1005 at Abstract; *see also id.* at [0010]-[0012], [0017], [0025], [0068]-[0069], [0073], [0081], [0096], [0101], Figs. 5B-5C, cls. 1-16. The '608 Publication also notes that “Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012]. The '608 Publication teaches limitations of [5a].

H. Anticipation of Claim 6 — Element by Element Claim Analysis

1. [6pre] The pharmaceutical product of claim 1,

244. The '608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [6pre]. *Supra* Section X.C.

2. **[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).**

245. The '608 Publication discloses storage stable lyophilized compositions of phenobarbital sodium salt with high purity that are essentially void of impurities upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1005 at Abstract, [0002], [0101], [0119]; *see also id.* at [0006]-[0007], [0009], [0025], [0071], [0096], [0106], cl. 16. The '608 Publication further discloses that the lyophilized phenobarbital sodium compositions “do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073]; *see also id.* at Abstract, [0006]-[0007], [0017], [0023]. Once the lyophilized phenobarbital sodium has been reconstituted after storage “for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC),” the '608 Publication discloses that the reconstituted solution forms “no more than 0.1% phenylethylacetylurea (PEAU).” *Id.* at [0016], [0088]; *see also id.* at [0013], [0024], [0071], [0082], [0089], [0091]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 7-13, 16, cls. 2, 8-9, 11-12; *see supra* Section X.D.2. The '608 Publication notes that “at least 6 months under accelerated stability conditions which is equivalent to 24 months at [room temperature].” *Id.* at [0017], [0071], [0091], [0101]; *see also id.* at cl. 11.

The compositions of the '608 Publication inherently disclose stability for up to 24 months.

246. This inherent disclosure was confirmed by the Applicant of the '608 Publication in the '914 CIP application as it provided 24-month stability data showing that the exact same batch of 65 mg/vial lyophilized phenobarbital sodium disclosed in the '608 Publication (Batch# NPH2020) exhibited the recited stability when reconstituted after being stored at room temperature for 24 months.

247. Specifically, the '914 CIP application discloses that Batch# NPH2020, as before, formed below quantitation limit ($<0.05\%$) of PEAU and did not form any detectable amounts of 2EPM and PBG, with total degradation products remaining below quantitation limit after being stored at room temperature for 24 months and then reconstituted. *Compare* Ex-1005 at Table 10, *with* Ex-1007 at 49-50 (¶[00144], Table 18); Ex-1001 at Table 18.

248. The '914 CIP application discloses that another batch of 65 mg/vial lyophilized phenobarbital sodium (Batch# NPH1980) and a batch of 130 mg/vial lyophilized phenobarbital sodium (Batch# NPH1912), also disclosed in the '608 Publication, demonstrated similar stability when reconstituted after being stored at room temperature for 30 months and 37 months, respectively. *Compare* Ex-1005 at Table 16 and Table 3, *with* Ex-1007 at 51-53 (¶¶[00147]-[00150], Tables 20-21); Ex-1001 at Tables 20-21.

249. Consequently, the '608 Publication, either expressly or inherently, teaches limitations of [6a]. *See supra* Section X.D.2.

I. Anticipation of Claim 7 — Element by Element Claim Analysis

1. [7pre] A pharmaceutical product, comprising:

250. As I understand from Petitioner's counsel and as detailed in **Appendix B**, the preamble generally does not constitute a limitation and therefore does not limit the claims.

251. As previously described in Element [1pre], the '608 Publication discloses “pharmaceutical product[s] including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration” and therefore teaches the limitations of [7pre]. Ex-1005 at Abstract, [0002], [0026]; *see also id.* at [0009]-[0011], [0013], [0015]-[0020], [0023]-[0024], [0071], [0073]-[0075], [0081]-[0082], [0088]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 6-13, 16, cls. 1-2, 8-12; *supra* Section X.C.1.

2. [7a] a single use dose vial, and

252. As previously described in Element [1a], the '608 Publication teaches aliquoting phenobarbital sodium into “single use dose vials for lyophilization” and therefore teaches the limitations of [7a]. Ex-1005 at [0079] (“[T]o produce 65 mg or 130 mg doses of lyophilized Phenobarbital Sodium, a batch may be dissolved,

mixed, pH adjusted if necessary, and filtered and then aliquoted into single use dose vials for lyophilization.”); *see also id.* at cl. 15; *see supra* Section X.C.2

3. [7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

253. As previously described in Element [1b], the '608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg and therefore teaches the limitations of [7b]. Ex-1005 at [0025] (disclosing 65 mg, 130 mg, 100 mg, and 200 mg powder doses); *see also id.* at [0008], [0068]-[0069], [0075], [0079], [0093], [0099], [0102]-[0103], [0105]-[0106], [0119]-[0124], Figs. 5B-5C, Tables 1-3, 6-17, cls. 13, 19; *see supra* Section X.C.3.

4. [7c] wherein the composition is sterile and lyophilized,

254. As previously described in Element [1c], the '608 Publication teaches compositions of, methods of producing, and use of a lyophilized amorphous phenobarbital sodium formulation and filtering the phenobarbital sodium solution prior to lyophilization “to remove any foreign particles” and that phenobarbital sodium “solution may be aliquoted into sterile containers” and therefore teaches the limitations of [7c]. Ex-1005 at Abstract, [0002], [0010]-[0011], [0013], [0015]-[0020], [0023], [0025]-[0027], [0071], [0073]-[0075], [0078]-[0082], [0088]-

[0096], [0101]-[0108], [0120]-[0121], [0123]-[0124], Tables 1-3, 7-13, 15-17, cls. 1-2, 8-12, 14-16; *see supra* Section X.C.4.

5. [7d] wherein the composition comprises no less than 98% phenobarbital sodium, and

255. As previously described in Element [1d], the '608 Publication discloses that the lyophilized phenobarbital sodium contains “no less than 98% Phenobarbital Sodium” and therefore teaches the limitations of [7d]. Ex-1005 at [0010], [0024], [0071], [0103]-[0104], [0120]-[0121], [0124], Table 2-3, 7-13, 16; *see also id.* at Abstract, [0002]; *see supra* Section X.C.5.

6. [7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).

256. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

J. Anticipation of Claim 8 — Element by Element Claim Analysis

1. [8pre] The pharmaceutical product of claim 7,

257. The '608 Publication discloses the pharmaceutical product that teaches limitations of [7pre]-[7e], and therefore, it teaches limitations of [8pre]. *Supra* Section X.I.

2. **[8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.**

258. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

K. Anticipation of Claim 9 — Element by Element Claim Analysis

1. **[9pre] The pharmaceutical product of claim 7,**

259. The '608 Publication discloses the pharmaceutical product that teaches limitations of [7pre]-[7e], and therefore, it teaches limitations of [9pre].

Supra Section X.I.

2. **[9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).**

260. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

L. Anticipation of Claim 10 — Element by Element Claim Analysis

1. **[10pre] The pharmaceutical product of claim 7,**

261. The '608 Publication discloses the pharmaceutical product that teaches limitations of [7pre]-[7e], and therefore, it teaches limitations of [10pre].

Supra Section X.I.

2. **[10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).**

262. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

M. Anticipation of Claim 11 — Element by Element Claim Analysis

1. **[11pre] The pharmaceutical product of claim 10,**

263. The '608 Publication discloses the pharmaceutical product that teaches limitations of [10pre]-[10a], and therefore, it teaches limitations of [11pre].

Supra Section X.L.

2. **[11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).**

264. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

N. Anticipation of Claim 12 — Element by Element Claim Analysis

1. [12pre] The pharmaceutical product of claim 7,

265. The '608 Publication discloses the pharmaceutical product that teaches limitations of [7pre]-[7e], and therefore, it teaches limitations of [12pre].
Supra Section X.I.

2. [12a] wherein the composition is amorphous.

266. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a]. *See supra* Section X.G.2.

O. Anticipation of Claim 13 — Element by Element Claim Analysis

1. [13pre] The pharmaceutical product of claim 12,

267. The '608 Publication discloses the pharmaceutical product that teaches limitations of [12pre]-[12a], and therefore, it teaches limitations of [13pre].
Supra Section X.N.

2. [13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

268. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See infra* Section X.P.2.

P. Anticipation of Claim 14 — Element by Element Claim Analysis

1. [14pre] The pharmaceutical product of claim 1,

269. The '608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [14pre].

Supra Section X.C.

2. **[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).**

270. The '608 Publication discloses storage stable lyophilized compositions of phenobarbital sodium salt with high purity that are essentially void of impurities upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1005 at Abstract, [0002], [0101], [0119]; *see also id.* at [0006]-[0007], [0009], [0025], [0071], [0096], [0106], cl. 16. The '608 Publication further discloses that the lyophilized phenobarbital sodium compositions “do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073]; *see also id.* at Abstract, [0006]-[0007], [0017], [0023]. The '608 Publication further discloses that “the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room

temperature] and accelerated stability conditions.” *Id.* at [0016]; *see also id.* at [0013], [0017], [0024], [0071], [0090]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 7-13, 16, cls. 10-12. The ’608 Publication further discloses that “the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.).” *Id.* at [0016]; *see also id.* at [0013], [0024], [0071], [0082], [0088]-[0089], [0091]-[0092], [0101], [0103]-[0104], [0120]-[0121], [0124], Tables 2-3, 7-13, 16, cls. 2, 8-9, 11-12. The ’608 Publication teaches limitations of [14a].

Q. Anticipation of Claim 15 — Element by Element Claim Analysis

1. [15pre] The pharmaceutical product of claim 14,

271. The ’608 Publication discloses the pharmaceutical product that teaches limitations of [14pre]-[14a], and therefore, it teaches limitations of [15pre]. *Supra* Section X.P.

2. [15a] wherein the composition is amorphous.

272. The ’608 Publication discloses this element for the reasons set forth with respect to Element [5a]. *See supra* Section X.G.2.

R. Anticipation of Claim 16 — Element by Element Claim Analysis

1. [16pre] The pharmaceutical product of claim 1,

273. The '608 Publication discloses the pharmaceutical product that teaches limitations of [1pre]-[1d], and therefore, it teaches limitations of [16pre].

Supra Section X.C.

2. [16a] wherein the product comprises the 100 mg dose in the single use dose vial.

274. The '608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 100 mg. Ex-1005 at [0025], [0079], [0099]; *see id.* at [0075], [0093], [0105], [0106], [0119], Tables 6, 17, cls. 13, 15, 19. The '608 Publication teaches limitations of [16a].

S. Anticipation of Claim 17 — Element by Element Claim Analysis

1. [17pre] The pharmaceutical product of claim 7,

275. The '608 Publication discloses the pharmaceutical product that teaches limitations of [7pre]-[7e], and therefore, it teaches limitations of [17pre].

Supra Section X.I.

2. [17a] wherein the product comprises the 100 mg dose in the single use dose vial.

276. The '608 Publication discloses this element for the reasons set forth with respect to Element [16a]. *See supra* Section X.R.2.

T. Anticipation of Claim 18 — Element by Element Claim Analysis

1. [18pre] The pharmaceutical product of claim 8,

277. The '608 Publication discloses the pharmaceutical product that teaches limitations of [8pre]-[8a], and therefore, it teaches limitations of [18pre].

Supra Section X.J.

2. **[18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).**

278. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See supra* Section X.P.2.

U. Anticipation of Claim 19 — Element by Element Claim Analysis

1. **[19pre] The pharmaceutical product of claim 8,**

279. The '608 Publication discloses the pharmaceutical product that teaches limitations of [8pre]-[8a], and therefore, it teaches limitations of [19pre].

Supra Section X.J.

2. **[19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).**

280. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. *See supra* Section X.P.2.

V. Anticipation of Claim 20 — Element by Element Claim Analysis

1. [20pre] The pharmaceutical product of claim 8,

281. The '608 Publication discloses the pharmaceutical product that teaches limitations of [8pre]-[8a], and therefore, it teaches limitations of [20pre].
Supra Section X.J.

2. [20a] wherein the composition is amorphous.

282. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a]. *See supra* Section X.G.2.

283. For these reasons, claims 1-20 are anticipated by the '608 Publication

XI. INVALIDITY GROUND 3: THE CHALLENGED CLAIMS ARE OBVIOUS OVER THE '608 PUBLICATION AND THE ORDINARY KNOWLEDGE OF A POSA

284. The Original Applications lack sufficient written description of the full scope of the challenged claims. *See supra* Section X.A. Consequently, the challenged claims are not entitled to a priority date earlier than June 30, 2022, the filing date of the '914 CIP application.

285. The '608 Publication was published on March 25, 2021, more than one year prior to June 30, 2022. Ex-1005 at cover. Accordingly, as I understand from Petitioner's counsel, the '608 Publication qualifies as § 102(a) prior art. In my opinion, the challenged claims are also obvious based on the '608 Publication alone in light of the ordinary knowledge of a person or ordinary skill in the art.

286. The challenged claims are divided into limitations as shown in

Appendix C.

287. An overview of the '608 Publication is provided in Section X.B above and is incorporated here.

A. Motivation to Make Lyophilized Phenobarbital Sodium Pharmaceutical Products Covered by the Challenged Claims with a Reasonable Expectation of Success

288. The challenged claims are directed to pharmaceutical products comprising lyophilized phenobarbital sodium compositions. Ex-1001 at cls. 1-20. Such pharmaceutical products, including highly pure, sterile, and stable lyophilized phenobarbital sodium formulations, were well known in the art.

289. The '608 Publication discloses the same pharmaceutical products comprising highly pure, sterile, and stable lyophilized phenobarbital sodium compositions, which a POSA would have been motivated to develop. *See generally* Ex-1005. Specifically, the '608 Publication describes amorphous lyophilized phenobarbital sodium formulations that purportedly achieve “surprising, unexpected and desirable results,” including enhanced stability and reduced impurities compared to prior art formulations. *Id.* at [0011].

290. A POSA would have recognized the claimed advantages of lyophilization for achieving these outcomes, particularly its ability to reduce residual moisture, which minimizes hydrolysis and the formation of toxic

degradants such as PEAU, 2EPMM, and PBG. *See id.* at [0005]-[0007], [0011], [0016]-[0017], [0023]-[0024], [0073]. Given the known challenges of hydrolysis and impurity formation in phenobarbital sodium compositions, a POSA would have been motivated to adopt the techniques disclosed in the '608 Publication to create highly pure and stable compositions.

291. A POSA would have been motivated to develop a lyophilized pharmaceutical product to improve the stability and shelf life of phenobarbital sodium compositions. Lyophilization, a well-established technique in pharmaceutical manufacturing, removes water through freezing and sublimation under vacuum. A POSA would have understood that this process stabilizes moisture-sensitive APIs like phenobarbital sodium by reducing hydrolysis, a primary degradation pathway. Ex-1005 at [0006]-[0007], [0073], [0075]. The '608 Publication emphasizes that its lyophilized compositions are storage-stable for at least six months at room temperature and under accelerated conditions (at 40°C, 75% RH), equivalent to 24 months at room temperature. *See supra* Sections X.D-F, X.H-M, X.O-P, X.T-U.

292. A POSA would have recognized the importance of extending shelf life to ensure pharmaceutical products remain effective over prolonged periods. Given the susceptibility of phenobarbital sodium to degradation through hydrolysis, a POSA would have been motivated to ensure the composition had a shelf life of at

least two years and, as a matter of routine, would have monitored and tested the stability of the batches for at least that duration. In doing so, the POSA would have implemented strategies to maximize stability and minimize impurities, ensuring a long shelf life and maintaining therapeutic efficacy. The ability to achieve storage stability equivalent to at least 24 months at room temperature would have been particularly desirable for products intended for global distribution, where storage and transportation conditions can vary significantly. A POSA would have sought to create formulations capable of withstanding these conditions while maintaining minimal levels of impurities, such as PEAU, 2EPMM, and PBG, upon reconstitution with 10 mL of an aqueous solution.

293. The '608 Publication also discloses that its lyophilized phenobarbital sodium products are amorphous and sterile. *See supra* Sections X.C, X.G, X.I, X.N, X.Q, X.V. A POSA would have known that lyophilization, particularly through rapid freezing, can enable the conversion of a crystalline drug to an amorphous state. *See supra* Section VII.C. This process, combined with the teachings of the '608 Publication, would have motivated a POSA to produce an amorphous phenobarbital sodium composition.

294. Moreover, a POSA would have understood the importance of sterility in injectable formulations. Recognizing that lyophilized phenobarbital sodium is typically administered intravenously or intramuscularly, a POSA would have

understood the critical need for sterility to ensure safety. *See* Ex-1005 at [0005], [0079]. The '608 Publication teaches that the phenobarbital sodium solution can be filtered prior to lyophilization and that phenobarbital sodium solution may be aliquoted into sterile containers. *See supra* Sections X.C, X.I. These practices, widely known in the art, are commonly used for producing pharmaceutical products intended for intravenous or intramuscular administration.

295. The '608 Publication also discloses specific single-use dosages of 65 mg, 100 mg, 130 mg, and 200 mg of lyophilized phenobarbital sodium. *See supra* Sections X.C, X.I, X.R-S. A POSA would have been motivated to adopt these dosages, as single-use vials minimize contamination risks and ensure precise dosing in clinical settings. Single-use dosage form is also particularly advantageous for injectable formulations, where sterility and accurate dosing are paramount to patient safety.

296. The '608 Publication further discloses that its lyophilized compositions achieve high purity (no less than 98%) with minimal drug degradation. *See supra* Sections X.C, X.I. A POSA would have recognized that the purity of a drug product is critical for safety and efficacy, especially for intravenous or intramuscular administration, where even trace impurities can cause adverse effects. *See* Ex-1005 at [0005]. By reducing residual moisture through lyophilization, a POSA would have minimized hydrolysis and control degradants.

The '608 Publication teaches that its formulations, upon reconstitution, contain no more than 0.05% PEAU and undetectable levels of 2EPMM and PBG after storage, demonstrating the effectiveness of its approach in controlling impurities. *See supra* Sections X.D-F, X.H-M, X.O-P, X.T-U.

297. Lyophilization also provides a well-established method for managing impurities. A POSA would have been motivated to adopt techniques such as sterile filtration of prelyophilization solution, aseptic processing, and stoppering within the freeze-dryer to ensure that the final product was sterile and met stringent purity standards. The '608 Publication's data demonstrating low levels of impurities after reconstitution would have further incentivized a POSA to adopt its disclosed methods to develop a highly pure and stable lyophilized product.

298. Additionally, a POSA would have been familiar with established impurity control strategies, including optimizing process parameters, controlling residual moisture levels, and conducting forced degradation studies to understand, predict and mitigate impurity formation. These techniques, aligned with the teachings of the '608 Publication, would have provided a clear pathway for achieving the high-purity, stable compositions disclosed.

299. Given the teachings of the '608 Publication and the general knowledge of a POSA, there would have been ample motivation to develop pharmaceutical products comprising lyophilized phenobarbital sodium

compositions covered by the challenged claims. The disclosures in the '608 Publication, combined with well-known principles of lyophilization, impurity control, and sterile manufacturing, would have enabled a POSA to create such compositions with a reasonable expectation of success. Consequently, the challenged claims are rendered obvious in light of the '608 Publication and the knowledge of a POSA.

B. Obviousness of Claim 1 — Element by Element Claim Analysis

1. [1pre] A storage stable pharmaceutical product, comprising:

300. As I understand from Petitioner's counsel and as detailed in **Appendix B**, the preamble generally does not constitute a limitation and therefore does not limit the claims.

301. The '608 Publication discloses this element for the reasons set forth with respect to Element [1pre] in Ground 2. *See supra* Section X.C.1.

302. Furthermore, the successful development of storage-stable phenobarbital sodium pharmaceutical products as discussed in the '608 Publication clearly demonstrates that a POSA would have been aware of the viability and effectiveness of phenobarbital sodium into a storage stable pharmaceutical product. Thus, a POSA would have been motivated, with a reasonable expectation of success, to produce such a storage-stable phenobarbital sodium composition. In view of the disclosures above, the '608 Publication meets element [1pre].

2. [1a] a single use dose vial, and

303. The '608 Publication discloses this element for the reasons set forth with respect to Element [1a] in Ground 2. *See supra* Section X.C.2.

304. Furthermore, a POSA would have recognized the substantial benefits that single-dose packaging provides for both patients and healthcare professionals. Single use vials ensure that each dose is sterile and accurately measured, eliminates the risk of contamination associated with multidose vials and thereby ensures patient safety. *See supra* Section VII.B. In view of the disclosures above, the '608 Publication meets element [1a].

3. [1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

305. The '608 Publication discloses this element for the reasons set forth with respect to Element [1b] in Ground 2. *See supra* Section X.C.3.

306. Furthermore, the '608 Publication demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 65 mg, 100 mg, 130 mg, or 200 mg is feasible. A POSA would have recognized that using these well-accepted dosages would minimize formulation challenges, as their efficacy and safety profiles are already known. In view of the disclosures above, the '608 Publication meets element [1b].

4. [1c] wherein the composition is sterile and lyophilized, and

307. The '608 Publication discloses this element for the reasons set forth with respect to Element [1c] in Ground 2. *See supra* Section X.C.4.

308. Furthermore, the successful development of lyophilized phenobarbital sodium products as discussed in the '608 Publication clearly demonstrates that a POSA would have been aware of the viability and effectiveness of lyophilizing phenobarbital sodium. Thus, a POSA would have been motivated, with a reasonable expectation of success, to produce such a lyophilized phenobarbital sodium composition.

309. Additionally, the '608 Publication further teaches that lyophilized phenobarbital sodium drug compositions can be sterile. By aliquoting the filtered solution into sterile vials prior to lyophilization, the '608 Publication highlights an effective method for producing sterile lyophilized drug products, further supporting the feasibility and practicality of creating sterile phenobarbital sodium compositions. In view of the disclosures above, the '608 Publication meets element [1c].

5. [1d] wherein the composition comprises no less than 98% phenobarbital sodium.

310. The '608 Publication discloses this element for the reasons set forth with respect to Element [1d] in Ground 2. *See supra* Section X.C.5.

311. Given the documented success of stable formulations like the lyophilized phenobarbital sodium disclosed in the '608 Publication, a POSA would recognize that it is not only possible but also desirable and advantageous to develop a lyophilized amorphous phenobarbital sodium composition containing at least 98% phenobarbital sodium. The practicality, stability, and safety of compositions disclosed in the '608 Publication exemplify the benefits of such high-purity formulations, motivating a POSA to pursue this approach with a reasonable expectation of success. In view of the disclosures above, the '608 Publication meets element [1d].

312. For these reasons, claim 1 is obvious over the '608 Publication.

C. Obviousness of Claim 2 — Element by Element Claim Analysis

1. [2pre] The pharmaceutical product of claim 1,

313. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. [2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

314. The '608 Publication discloses this element for the reasons set forth with respect to Element [2a] in Ground 2. *See supra* Section X.D.2.

315. The '608 Publication also discloses that the stability of solubilized phenobarbital sodium is a “recurring problem” as it “readily hydrolyzes in water forming various [toxic] degradation products.” Ex-1005 at [0005]-[0006]. The '608 Publication teaches that “in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) . . . [that] are toxic and cause severe side effects.” Ex-1005 at [0006]. The '608 Publication reports that “PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. . . . Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.” Ex-1005 at [0006]. Accordingly, a POSA would have known that phenobarbital sodium can degrade to produce harmful degradants such as PEAU, 2EPMM, and PBG. The well-documented degradation of phenobarbital sodium would have motivated a POSA to employ strategies to control and minimize toxic degradation products, ensuring the stability and safety of the pharmaceutical formulation.

316. Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like the lyophilized phenobarbital sodium disclosed in the '608 Publication, a POSA would understand that lyophilized phenobarbital sodium drug product, after storage for six months at 40° C, would form no more than 0.1% PEAU when reconstituted for injection with 10 mL of an aqueous solution and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. In view of the disclosures above, the '608 Publication meets element [2a], and claim 2 is obvious over the '608 Publication.

D. Obviousness of Claim 3 — Element by Element Claim Analysis

1. [3pre] The pharmaceutical product of claim 1,

317. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. [3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.

318. The '608 Publication discloses this element for the reasons set forth with respect to Element [3a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.E.2; *see infra* Section XI.O.2.

E. Obviousness of Claim 4 — Element by Element Claim Analysis

1. [4pre] The pharmaceutical product of claim 1,

319. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. [4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

320. The '608 Publication discloses this element for the reasons set forth with respect to Element [4a] in Ground 2. *See supra* Section X.F.2.

321. The '608 Publication also discloses that the stability of solubilized phenobarbital sodium is a “recurring problem” as it “readily hydrolyzes in water forming various [toxic] degradation products.” Ex-1005 at [0005]-[0006]. The '608 Publication teaches that “in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) . . . [that] are toxic and cause severe side effects.” Ex-1005 at [0006]. The '608 Publication reports that “PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic

effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. . . . Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.” Ex-1005 at [0006]. Accordingly, a POSA would have known that phenobarbital sodium can degrade to produce harmful degradants such as PEAU, 2EPMM, and PBG. The well-documented degradation of phenobarbital sodium would have motivated a POSA to employ strategies to control and minimize toxic degradation products, ensuring the stability and safety of the pharmaceutical formulation.

322. Given the extensive knowledge of phenobarbital sodium’s degradation pathways and the documented success of stable formulations like the lyophilized phenobarbital sodium disclosed in the ’608 Publication, a POSA would understand that lyophilized phenobarbital sodium drug product, after storage for six months at 40° C, would form no more than 0.05% of 2EPMM or PBG when reconstituted for injection with 10 mL of an aqueous solution and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. In view of the disclosures above, the ’608 Publication meets element [4a], and claim 4 is obvious over the ’608 Publication.

F. Obviousness of Claim 5 — Element by Element Claim Analysis

1. [5pre] The pharmaceutical product of claim 1,

323. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. [5a] wherein the composition is amorphous.

324. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a] in Ground 2. *See supra* Section X.G.2.

325. Given the documented success of stable formulations like the lyophilized amorphous phenobarbital sodium disclosed in the '608 Publication, a POSA would recognize that the lyophilized phenobarbital sodium composition would be amorphous. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms would guide a POSA in developing a stable and effective lyophilized amorphous phenobarbital sodium composition. In view of the disclosures above, the '608 Publication meets element [5a], and claim 5 is obvious over the '608 Publication.

G. Obviousness of Claim 6 — Element by Element Claim Analysis

1. [6pre] The pharmaceutical product of claim 1,

326. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. **[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).**

327. The '608 Publication discloses this element for the reasons set forth with respect to Element [6a] in Ground 2. *See supra* Section X.H.2.

328. The '608 Publication also discloses that the stability of solubilized phenobarbital sodium is a “recurring problem” as it “readily hydrolyzes in water forming various [toxic] degradation products.” Ex-1005 at [0005]-[0006]. The '608 Publication teaches that “in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) . . . [that] are toxic and cause severe side effects.” Ex-1005 at [0006].

329. The '608 Publication reports that “PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. . . . Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.” Ex-1005 at [0006].

330. Accordingly, a POSA would have known that phenobarbital sodium can degrade to produce harmful degradants such as PEAU, 2EPMM, and PBG. The well-documented degradation of phenobarbital sodium would have motivated a POSA to employ strategies to control and minimize toxic degradation products, ensuring the stability and safety of the pharmaceutical formulation.

331. Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like the lyophilized phenobarbital sodium disclosed in the '608 Publication, a POSA would understand that lyophilized phenobarbital sodium drug product would form at most 0.1% PEAU when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 24 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition.

332. A POSA would also be motivated to ensure that a lyophilized phenobarbital sodium drug product is storage-stable for 24 months, as an extended shelf life provides increased flexibility in storage, transportation, and distribution—factors important for maintaining a reliable drug supply chain. Longer shelf stability reduces the frequency of manufacturing and replenishment, ultimately lowering costs and improving patient access, particularly in regions with challenges in supply chain. Moreover, achieving 24-month stability offers a

substantial margin of assurance regarding drug quality, efficacy, and safety over time, which is highly desirable from both regulatory and commercial perspectives.

333. In view of the disclosures above, the '608 Publication meets element [6a], and claim 6 is obvious over the '608 Publication.

H. Obviousness of Claim 7 — Element by Element Claim Analysis

1. [7pre] A pharmaceutical product, comprising:

334. As I understand from Petitioner's counsel and as detailed in **Appendix B**, the preamble generally does not constitute a limitation and therefore does not limit the claims.

335. The '608 Publication discloses this element for the reasons set forth with respect to Element [7pre] in Ground 2 and Element [1pre] in Ground 3. *See supra* Sections X.I.1, XI.B.1.

336. The successful development of phenobarbital sodium products as discussed in the '608 Publication clearly demonstrates that a POSA would have been aware of the viability and effectiveness of phenobarbital sodium into a pharmaceutical product. Thus, a POSA would have been motivated, with a reasonable expectation of success, to produce such a phenobarbital sodium composition. In view of the disclosures above, the '608 Publication meets element [7pre].

2. [7a] a single use dose vial, and

337. The '608 Publication discloses this element for the reasons set forth with respect to Element [7a] in Ground 2 and Element [1a] in Ground 3. *See supra* Sections X.I.2, XI.B.2.

3. [7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

338. The '608 Publication discloses this element for the reasons set forth with respect to Element [7b] in Ground 2 and Element [1b] in Ground 3. *See supra* Sections X.I.3, XI.B.3.

4. [7c] wherein the composition is sterile and lyophilized,

339. The '608 Publication discloses this element for the reasons set forth with respect to Element [7c] in Ground 2 and Element [1c] in Ground 3. *See supra* Sections X.I.4, XI.B.4.

5. [7d] wherein the composition comprises no less than 98% phenobarbital sodium, and

340. The '608 Publication discloses this element for the reasons set forth with respect to Element [7d] in Ground 2 and Element [1d] in Ground 3. *See supra* Sections X.I.5, XI.B.5.

6. **[7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).**

341. The '608 Publication discloses this element for the reasons set forth with respect to Element [7e] in Ground 2 and Element [14a] in Ground 3. *See supra* Sections X.I.6; *see infra* Section XI.O.2.

I. Obviousness of Claim 8 — Element by Element Claim Analysis

1. **[8pre] The pharmaceutical product of claim 7,**

342. The '608 Publication discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section XI.H.

2. **[8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.**

343. The '608 Publication discloses this element for the reasons set forth with respect to Element [8a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.J.2; *see infra* Section XI.O.2.

J. Obviousness of Claim 9 — Element by Element Claim Analysis

1. [9pre] The pharmaceutical product of claim 7,

344. The '608 Publication discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section XI.H.

2. [9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

345. The '608 Publication discloses this element for the reasons set forth with respect to Element [9a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.K.2; *see infra* Section XI.O.2.

K. Obviousness of Claim 10 — Element by Element Claim Analysis

1. [10pre] The pharmaceutical product of claim 7,

346. The '608 Publication discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section XI.H.

2. [10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

347. The '608 Publication discloses this element for the reasons set forth with respect to Element [10a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.L.2; *see infra* Section XI.O.2.

L. Obviousness of Claim 11 — Element by Element Claim Analysis

1. [11pre] The pharmaceutical product of claim 10,

348. The '608 Publication discloses and renders obvious the limitations of [10pre]-[10a]. *Supra* Section XI.K.

2. [11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

349. The '608 Publication discloses this element for the reasons set forth with respect to Element [11a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.M.2; *see infra* Section XI.O.2.

M. Obviousness of Claim 12 — Element by Element Claim Analysis

1. [12pre] The pharmaceutical product of claim 7,

350. The '608 Publication discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section XI.H.

2. [12a] wherein the composition is amorphous.

351. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a] in Ground 2 and Element [5a] in Ground 3. *See supra* Sections X.G.2, XI.F.2.

N. Obviousness of Claim 13 — Element by Element Claim Analysis

1. [13pre] The pharmaceutical product of claim 12,

352. The '608 Publication discloses and renders obvious the limitations of [12pre]-[12a]. *Supra* Section XI.M.

2. [13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

353. The '608 Publication discloses this element for the reasons set forth with respect to Element [13a] in Ground 2 and Element [14a] in Ground 3. *See supra* Section X.O.2; *see infra* Section XI.O.2.

O. Obviousness of Claim 14 — Element by Element Claim Analysis

1. [14pre] The pharmaceutical product of claim 1,

354. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. **[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).**

355. The '608 Publication discloses this element for the reasons set forth with respect to Element [14a] in Ground 2. *See supra* Section X.P.2.

356. The '608 Publication also discloses that the stability of solubilized phenobarbital sodium is a “recurring problem” as it “readily hydrolyzes in water forming various [toxic] degradation products.” Ex-1005 at [0005]-[0006]. The '608 Publication teaches that “in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) . . . [that] are toxic and cause severe side effects.” Ex-1005 at [0006].

357. The '608 Publication reports that “PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. . . . Prior to its removal as an FDA-approved

drug, patients treated with Pheneturide showed low levels of serum calcium and folate.” Ex-1005 at [0006].

358. Accordingly, a POSA would have known that phenobarbital sodium can degrade to produce harmful degradants such as PEAU, 2EPMM, and PBG. The well-documented degradation of phenobarbital sodium would have motivated a POSA to employ strategies to control and minimize toxic degradation products, ensuring the stability and safety of the pharmaceutical formulation.

359. Given the extensive knowledge of phenobarbital sodium’s degradation pathways and the documented success of stable formulations like the lyophilized phenobarbital sodium disclosed in the ’608 Publication, a POSA would understand that lyophilized phenobarbital sodium drug product would form no more than 0.05% PEAU and no more than 0.05% of 2EPMM or PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. In view of the disclosures above, the ’608 Publication meets element [14a], and claim 14 is obvious over the ’608 Publication.

P. Obviousness of Claim 15 — Element by Element Claim Analysis

1. [15pre] The pharmaceutical product of claim 14,

360. The '608 Publication discloses and renders obvious the limitations of [14pre]-[14a]. *Supra* Section XI.O.

2. [15a] wherein the composition is amorphous.

361. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a] in Ground 2 and Element [5a] in Ground 3. *See supra* Sections X.G.2, XI.F.2.

Q. Obviousness of Claim 16 — Element by Element Claim Analysis

1. [16pre] The pharmaceutical product of claim 1,

362. The '608 Publication discloses and renders obvious the limitations of [1pre]-[1d]. *Supra* Section XI.B.

2. [16a] wherein the product comprises the 100 mg dose in the single use dose vial.

363. The '608 Publication discloses this element for the reasons set forth with respect to Element [16a] in Ground 2. *See supra* Section X.R.2.

364. The '608 Publication further demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 100 mg is feasible. A POSA would have recognized that using these well-accepted dosages would minimize formulation challenges, as their efficacy and safety profiles are already known. In

view of the disclosures above, the '608 Publication meets element [16a], and claim 16 is obvious over the '608 Publication.

R. Obviousness of Claim 17 — Element by Element Claim Analysis

1. [17pre] The pharmaceutical product of claim 7,

365. The '608 Publication discloses and renders obvious the limitations of [7pre]-[7e]. *Supra* Section XI.H.

2. [17a] wherein the product comprises the 100 mg dose in the single use dose vial.

366. The '608 Publication discloses this element for the reasons set forth with respect to Element [17a] in Ground 2 and Element [16a] in Ground 3. *See supra* Sections X.S.2, XI.Q.2.

S. Obviousness of Claim 18 — Element by Element Claim Analysis

1. [18pre] The pharmaceutical product of claim 8,

367. The '608 Publication discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section XI.I.

2. [18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

368. The '608 Publication discloses this element for the reasons set forth with respect to Element [18a] in Ground 2 and Element [14a] in Ground 3. *See supra* Sections X.T.2, XI.O.2.

T. Obviousness of Claim 19 — Element by Element Claim Analysis

1. [19pre] The pharmaceutical product of claim 8,

369. The '608 Publication discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section XI.I.

2. [19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

370. The '608 Publication discloses this element for the reasons set forth with respect to Element [19a] in Ground 2 and Element [14a] in Ground 3. *See supra* Sections X.U.2, XI.O.2.

U. Obviousness of Claim 20 — Element by Element Claim Analysis

1. [20pre] The pharmaceutical product of claim 8,

371. The '608 Publication discloses and renders obvious the limitations of [8pre]-[8a]. *Supra* Section XI.I.

2. [20a] wherein the composition is amorphous.

372. The '608 Publication discloses this element for the reasons set forth with respect to Element [5a] in Ground 2 and Element [5a] in Ground 3. *See supra* Sections X.G.2, XI.F.2.

373. For these reasons, the challenged claims are obvious over the '608 Publication

XII. OBVIOUSNESS – SECONDARY CONSIDERATIONS

374. Petitioner's counsel has informed me that one of the factual inquiries relevant to an obviousness analysis is objective indicia of non-obviousness, also called secondary considerations of non-obviousness, which include unexpected results, commercial success, long felt but unmet need, failure of others, copying by others, and skepticism of experts. The legal principles provided to me by Petitioner's counsel with respect to secondary considerations are in **Appendix B**.

375. Below I address certain statements made by Applicants in either the '076 Patent or the prosecution histories of the '076 Patent, the '914 CIP application, the '881 application, or the '511 application that were potentially directed to secondary considerations of non-obviousness and their applicability to Grounds 1 and 3. For the reasons I explain below, the evidence from the intrinsic record, considered in connection with my analysis of Grounds 1 and 3 above, does not change my opinion that challenged claims 1-20 are obvious.

376. The intrinsic evidence does not establish any secondary considerations. Any alleged secondary considerations (1) lack the required nexus to the full scope of claims 1-20 and (2) do not overcome the clear showing that claims 1-20 are obvious for the reasons I explained in Invalidity Grounds 1 and 3.

377. Specifically, during the prosecution of the '881 application, the Applicants submitted a declaration from Dr. Dasaradhi Lakkaraju, one of the named inventors⁹. Ex-1004 at 641-44 (Decl. of Dr. Dasaradhi Lakkaraju under 37 C.F.R. § 1.132). Dr. Lakkaraju states that “the storage performance of the lyophilized amorphous form of Phenobarbital Sodium is surprising and unexpected” because “[a] skilled artisan in the art would appreciate that the amorphous form of Phenobarbital Sodium lacks ordered crystalline structure and tight packing, which would normally prevent or substantially reduce degradation processes” and “[a]morphous forms do not provide such limitations and therefore would be normally considered as inferior to crystalline forms.” Ex-1004 at 643; *see also id.* at 636 (“[T]he claimed composition provided as a lyophilized amorphous powder form would not be normally expected to demonstrate superior storage stability as was unexpectedly discovered by the inventors of the present patent

⁹ Dr. Dasaradhi Lakkaraju’s name appears to have been misspelled in the declaration. *See* Ex-1004 at 641, 644; *see also* Ex-1001 at cover.

application.”), 196 (¶[0011]) (“These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material.”); Ex-1002 at 290 (“In particular, and as noted in Applicant’s specification, the claimed stability is particularly surprising and unexpected in view of the fact that conventional wisdom teaches that *crystalline material is more stable than amorphous material.*”) (emphasis in original). These statements do not support any claimed unexpected properties of the claimed formulations.

378. First, the Applicants do not provide any direct comparison between *lyophilized crystalline* phenobarbital sodium compositions and *lyophilized amorphous* phenobarbital sodium compositions to show unexpected superiority of the claimed amorphous form over its crystalline counterpart. The absence of a proper comparison prevents establishing a nexus between the claimed invention and any alleged unexpected results.

379. Second, as discussed in detail above, lyophilization is a well-known technique for improving stability and extending shelf life of pharmaceutical products. *See supra* Section VII.C. Given that phenobarbital sodium was known to be subject to hydrolysis, it would have been expected that lyophilization, which removes water, would reduce degradation products and lead to a more stable product. *See supra* Sections VII.A, VII.C, XI. This is a predictable outcome of

applying a known technique (lyophilization) to a known compound (phenobarbital sodium) to yield expected results (improved stability).

380. Third, it is important to note that the '608 Publication discloses the *same* storage-stable, lyophilized phenobarbital sodium compositions and products of the '076 Patent¹⁰, further demonstrating that any results claimed by the Applicants are not unexpected relative to the prior art. *See supra* Sections X-XI. As such, there are no secondary considerations of non-obviousness.

381. I reserve the right to address any secondary considerations put forth by the Patent Owners in any later response to this declaration or the petition.

XIII. THE PETITION SHOULD NOT BE DISCRETIONARILY DENIED

382. I understand from Petitioner's counsel that the Board may elect not to institute a proceeding (and discretionarily deny an IPR petition) if the challenge to

¹⁰ The batch numbers of phenobarbital sodium products in the '608 Publication are identical to the batch numbers in the '076 Patent. *See, e.g.*, Ex-1005 at Table 2 (Batch #NPH1907), Table 3 (Batch #NPH1912), Table 6 (Batch #NPH2031A), Table 8 (Batch #NPH2031B), Table 9 (Batch #NPH2030), Table 10 (Batch #NPH2020); Ex-1001 at Table 2 (Batch #NPH1907), Table 3 (Batch #NPH1912), Table 6 (Batch #NPH2031A), Table 8 (Batch #NPH2031B), Table 9 (Batch #NPH2030), Table 10 (Batch #NPH2020).

the patent is based on the same or substantially the same prior art or arguments previously presented to the Patent Office during prosecution. I further understand that this decision is based on a factual inquiry which considers the following, nonexclusive factors:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

383. Petitioner's counsel has informed me that these factors are considered in a two-part framework. First, factors (a), (b), and (d) above are considered to

determine whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Patent Office during prosecution. If the Board determines that the same or substantially the same art or arguments were previously presented to the Patent Office during prosecution, then factors (c), (e), and (f) above are considered to determine whether the Petitioner has demonstrated a material error by the Patent Office.

A. Part 1: The Same or Substantially the Same Art and Arguments Were Not Previously Presented to the Patent Office

384. The art and arguments discussed in Grounds 1-3 above are not the same or substantially the same as those previously presented to the Patent Office during prosecution. In reaching this conclusion, I considered factors (a), (b), and (d) above.

1. Factor (a): The Similarities and Material Differences Between the Asserted Art and the Prior Art Involved During Examination

385. During the prosecution of the '076 Patent (and its parent filings), the Examiner primarily relied on Parker—disclosing liquid phenobarbital sodium formulations containing organic solvents—to assess novelty and obviousness. *See* Ex-1002 at 270-71; Ex-1004 at 434-39, 650-56, 1152-57. In contrast, the lead

references underlying Grounds 1-3, namely PIF¹¹ (for obviousness in view of Parker and West-Ward) and the '608 Publication (for anticipation or obviousness), were never substantively evaluated. Neither the Examiner nor the Patent Owner addressed whether the lyophilized phenobarbital sodium formulations disclosed in the '608 Publication or PIF rendered the claims unpatentable. Accordingly, the claims' scope—including compositions containing crystalline forms or organic solvents—was never tested against the prior art now cited, all of which predates the relevant priority date. Thus, there are substantial, material differences between (i) the references reviewed by the Examiner (chiefly Parker) and (ii) the newly asserted references ('608 Publication, PIF, West-Ward), which disclose different formulations, different dosage forms, and different impurity profiles. Notably, like

¹¹ During the prosecution of the '511 application, there was a Third-Party Submission of Prior Art Under 37 C.F.R. § 1.290, in which Nobelbar—the focus of PIF—was identified. Ex-1004 at 826-54. The Examiner found that the third-party submission complied with 35 U.S.C. § 122(e) and 37 C.F.R. § 1.290 and allowed the submission to be entered into the '511 application. Ex-1004 at 1145. However, none of the twenty prior art references identified in the Third-Party Submission were addressed, discussed, or substantively considered by either the Examiner or the Applicants. *See generally* Ex-1004.

Parker, none of the other references relied on by the Examiner for § 102 and § 103 rejections—including Sun (Ex-1042), Kelly (Ex-1043), Snyder (Ex-1044), Dietz (Ex-1045), Roskos (Ex-1046), and FDA_7/93 (Ex-1047)—disclose highly pure, storage-stable, lyophilized phenobarbital sodium formulations without organic solvents. This stands in contrast to PIF and the '608 Publication, which specifically address storage-stable, lyophilized phenobarbital sodium compositions, further highlighting the material differences between the previously examined art and the newly asserted references.

2. Factor (b): The Cumulative Nature of the Lead Asserted Art and the Prior Art Evaluated During Examination

386. The asserted art is not cumulative of the prior art evaluated during examination. None of the references addressed and evaluated by the Examiner during the prosecution of the '076 patent (and parent filings) disclose highly pure, storage-stable, lyophilized phenobarbital sodium compositions without organic solvents. Notably, Parker's teachings are materially different from those of the '608 Publication and PIF because Parker focuses on a liquid phenobarbital sodium formulation containing organic solvents, whereas the '608 Publication and PIF disclose highly pure, lyophilized phenobarbital sodium compositions with distinct impurity controls and stability characteristics. Furthermore, West-Ward discloses recognized single-use dosages (e.g., 65 mg, 130 mg), again not explicitly accounted for by Parker alone. Because none of these references—individually or

in combination—were before the Examiner, the newly asserted grounds cannot be considered cumulative; the '608 Publication and PIF rely on entirely different teachings that had not been considered, addressed, or overcome in any prior prosecution record.

387. Moreover, the Examiner of the '076 patent did not identify the '608 Publication as prior art during the examination process. As a result, the Applicants' own storage-stable, lyophilized phenobarbital sodium compositions without organic solvents disclosed in the '608 Publication were not addressed at all.

388. The asserted grounds introduce new considerations and teachings that were not previously examined or addressed. The asserted art is not cumulative; rather, it presents a fundamentally different invalidity case compared to the prior art evaluated during the original examination of the '076 Patent and its parent filings.

3. Factor (d): The Extent of the Overlap Between the Arguments Made During Examination and the Manner in Which Petitioner Relies on the Prior Art or Patent Owners Distinguish the Prior Art

389. There is negligible overlap between the arguments made during prosecution and the manner in which Petitioner now relies on the newly asserted references. The record shows that the Examiner allowed the claims over Parker only after the applicants highlighted to the Examiner, among other things, that unlike the claimed compositions, Parker includes stabilizing co-solvents and

therefore its formulation will not produce a composition comprising more than 98% phenobarbital sodium. Ex-1002 at 288-90, 294, 296. The Examiner did not evaluate or discuss (1) the '608 Publication's detailed disclosures of lyophilized phenobarbital sodium compositions, (2) PIF's freeze-dried phenobarbital sodium, or (3) West-Ward's dosage forms. Hence, Petitioner's unpatentability contentions are new. They differ materially from any arguments previously before the Patent Office, which never examined these references for unpatentability.

390. Similarly, the Patent Office did not substantively address whether the Original Applications provided written description of the full scope of compositions containing organic solvents or crystalline phenobarbital sodium. The only §112-related issue the Examiner raised concerned “the drying step [of lyophilization] without the use of a vacuum,” which the Applicant addressed by canceling the relevant claim language. Ex-1002 at 269. At no point did the Examiner evaluate whether the challenged claims are fully supported by disclosures of the Original Applications pertaining to organic solvents or crystalline forms, matters that the Patent Owner only introduced later in the '914 CIP application. Consequently, the newly raised written-description issues—including the argument that the challenged claims can only claim priority to June 30, 2022—were never considered let alone decided on the merits.

391. Because the priority of the '076 Patent was never substantively addressed during prosecution, the Examiner did not evaluate whether the '608 Publication qualifies as prior art. The determination of whether the '608 Publication qualifies as prior art is central to Petitioner's unpatentability arguments. *See supra* Sections X-XI. But this issue was not part of the original examination and, therefore, represents a significant departure from the arguments previously considered by the Patent Office.

392. For the reasons explained above, the art and arguments in this declaration are not the same or substantially the same as those evaluated on the merits during prosecution of the '076 Patent (or the '914 CIP application). Therefore, the Board should not discretionarily deny the petition.

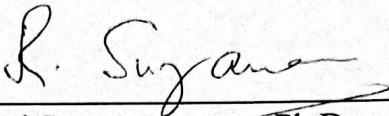
XIV. AVAILABILITY FOR CROSS EXAMINATION

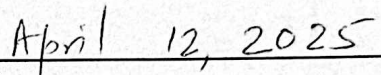
393. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, and with reasonable notice, I will appear for cross examination within the United States during the time allotted for cross examination.

394. I hereby declare that all statements made herein of 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 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declaration of Dr. Suryanarayanan for *Inter Partes* Review of U.S. Patent No. 11,878,076

I declare under penalty of perjury under the laws of the United States of America
that the foregoing is true and correct.


Raj Suryanarayanan, Ph.D.


Date

Appendix A

Exhibit No.	Exhibit Description
1001	U.S. Patent No. 11,878,076
1002	File History of U.S. Appl. No. 18/100,804
1003	File History of Provisional U.S. Appl. No. 62/903,511
1004	File History of Non-Provisional U.S. Appl. No. 17/025,881
1005	U.S. Publication No. 2021/0085608 A1 (the “’608 Publication”)
1006	U.S. Patent No. 11,406,598
1007	File History of U.S. Appl. No. 17/854,914
1008	An Internet Archive capture of <i>Pharmaceutical Interview Form</i> , NOBELPHARMA CO. (revised July 2010), https://web.archive.org/web/20110313193709/http://www.nobelpharma.co.jp:80/medical/pdf/Nobelbar/interviewform.pdf (“PIF”)
1009	English Translation of Pharmaceutical Interview Form (Ex-1008)
1010	Declaration of Ryan Bernasch for Translation of Pharmaceutical Interview Form (Ex-1008)
1011	Internet Archive Declaration of Pharmaceutical Interview Form (Ex-1008)
1012	U.S. Patent Application Publication No. US 2017/0143719 (“Parker”)
1013	An Internet Archive capture of <i>Label: PHENOBARBITAL SODIUM - phenobarbital sodium injection</i> , DAILYMED (updated August 2011), https://web.archive.org/web/20151004050809/http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ffcaa218-ed6a-4557-9645-b9a91128a214 (“West-Ward”)
1014	Internet Archive Declaration of West-Ward (Ex-1013)
1015	Declaration of Raj Suryanarayanan, Ph.D.
1016	Curriculum Vitae of Dr. Raj Suryanarayanan
1017	Excerpts of USP 40 — NF 35: THE UNITED STATES PHARMACOPEIA AND NATIONAL FORMULARY VOL. 1, U.S. PHARMACOPEIAL CONVENTION (2017)
1018	Sakthivel Lakshmana Prabu & T.N.K. Suriyaprakash, <i>Impurities and Its Importance in Pharmacy</i> , 3(2) INT. J. PHARM. SCI. REV. RES. 66 (2010)
1019	Jane D. Siegel et al., <i>2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings</i> , 35 AM. J. INFECT. CONTROL S65-164 (2007)

Exhibit No.	Exhibit Description
1020	<i>Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry</i> , U.S. FOOD AND DRUG ADMINISTRATION (Oct. 2018)
1021	Joanne Broadhead, <i>Parenteral Dosage Forms</i> , in PHARMACEUTICAL PREFORMULATION AND FORMULATION: A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 331 (Mark Gibson ed., 2001)
1022	NEAL G. ANDERSON, PRACTICAL PROCESS RESEARCH & DEVELOPMENT (1st ed. 2000)
1023	NEAL G. ANDERSON, PRACTICAL PROCESS RESEARCH & DEVELOPMENT (2d ed. 2012)
1024	Dejan S. Przic et al., <i>Lyophilization — The Process and Industrial Use</i> , 58(12) CHEM. IND. 552 (2004)
1025	Duncan Q.M. Craig et al., <i>The relevance of the amorphous state to pharmaceutical dosage forms: glassy drugs and freeze dried systems</i> , 179 INT. J. PHARM. 179 (1999)
1026	Michael J. Pikal, <i>Freeze Drying</i> , in ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY VOL. 1, 1807-33 (James Swarbrick ed., 3rd ed. 2007)
1027	FREEZE-DRYING/LYOPHILIZATION OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS (Louis Rey & Joan C. May eds., 3d ed. 2010)
1028	Tomaž Einfalt et al., <i>Methods of amorphization and investigation of the amorphous state</i> , 63 ACTA PHARM. 305 (2013)
1029	POLYMORPHISM IN PHARMACEUTICAL SOLIDS (Harry G. Brittain ed., 1999)
1030	JOEL BERNSTEIN, POLYMORPHISM IN MOLECULAR CRYSTALS (2002)
1031	Lian Yu, <i>Amorphous pharmaceutical solids: preparation, characterization and stabilization</i> , 48 ADV. DRUG DELIV. REV. 27 (2001)
1032	Pradip Hiwale et al., <i>Variables Affecting Reconstitution Time of Dry Powder for Injection</i> , PHARMACEUTICAL TECHNOLOGY 32:7 (July 2, 2008), https://www.pharmtech.com/view/variables-affecting-reconstitution-time-dry-powder-injection

Exhibit No.	Exhibit Description
1033	John K. Haleblan, <i>Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications</i> , 64(8) J. PHARM. SCI. 1269 (1975)
1034	<i>Annex 10: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products</i> , in WHO TECHNICAL REPORT SERIES No. 1010, WORLD HEALTH ORGANIZATION 309-51 (2018)
1035	<i>ICH Topic Q1A Stability Testing Guidelines: Stability Testing of New Drug Substances and Products - Step 5</i> , CPMP/ICH/380/95, EMEA (1995)
1036	<i>Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products</i> , U.S. FDA (Nov. 2003)
1037	Sun Hee Kim et al., <i>Physicochemical Stability of Reconstituted Decitabine (Dacogen®) Solutions and Ready-to-Administer Infusion Bags when Stored Refrigerated or Frozen</i> , 2(4) PHARM. TECHNOL. HOSP. PHARM. 145 (2017)
1038	Takuya Iwamoto et al., <i>Performance evaluation of the compounding robot, APOTECachemo, for injectable anticancer drugs in a Japanese hospital</i> , J. PHARM. HEALTH CARE SCI. 3:12 (2017)
1039	U.S. Patent No. 9,138,456
1040	Kou Kawada et al., <i>A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures</i> , 42(4) JPN. J. CLIN. PHARMACOL. THER. 205 (2011)
1041	Jumpei Saito et al., <i>Potentially Harmful Excipients in Neonatal Medications: An Observational and Cross-Regional Comparison of Japan and Europe</i> , 4(2) NEONAT. PEDIATR. MED. 172 (2018)
1042	U.S. Patent Appl. No. 2010/0035904 A1
1043	An Internet Archive capture of Lynne Kelly, <i>Phenobarbital sodium</i> , CRITICAL CARE TRAUMA CENTRE (last update: Oct. 11, 2018), https://web.archive.org/web/20220625233910/https://www.lhsc.on.ca/critical-care-trauma-centre/phenobarbital-sodium
1044	Meg Snyder, <i>Lyophilization: The basics</i> , DRUG DISCOVERY & DEVELOPMENT (Mar. 7, 2017), https://www.drugdiscoverytrends.com/lyophilization-the-basics/
1045	Nancy J. Dietz et al., <i>Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs</i> , 5(12) PHARM. RES. 803 (1988)
1046	U.S. Patent No. 6,077,545

Exhibit No.	Exhibit Description
1047	<i>Lyophilization of Parenteral (7/93): Guide to Inspections of Lyophilization of Parenterals</i> , U.S. FOOD AND DRUG ADMINISTRATION (1993), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793
1048	Petitioner's Motion to Dismiss For Improper Venue or, in the Alternative, Transfer, <i>Nivagen, Inc. v. Sun Pharms. Indus., Inc.</i> , No. 2:24-cv-00036-RWS-RSP, ECF No. 19 (E.D. Tex. June 27, 2024)
1049	USPTO Patent Assignment Database Entry for U.S. Patent No. 11,878,076, https://assignment.uspto.gov/patent/index.html#/patent/search/resultAbstract?id=11878076&type=patNum
1050	U.S. Patent No. 11,878,076 - Highlighted

Appendix B

1. I am not a lawyer and do not offer any legal opinion in my declaration. Petitioner's counsel has advised me on legal standards relevant to the technical matters I address, and I have applied those standards in forming the conclusions expressed in my declaration.

I. Claim Construction

2. I have been informed by Petitioner's counsel that the words of a patent claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art ("POSA") at the time of the invention. I am further informed that claim terms are construed in light of the claim language, the patent specification (including figures, tables, and examples), and the prosecution history (including references cited during prosecution).

II. Preamble

3. I have been informed by Petitioner's counsel that, as a general rule, the preamble of a patent claim is not considered limiting, especially where the body of the claim defines a structurally complete invention and the preamble merely states a purpose or intended use.

III. Anticipation

4. I have been informed by Petitioner's counsel that a prior art reference "anticipates" a claim, rendering it invalid, if all elements of the claim are disclosed in that reference and arranged as they are in the claim.

5. I have also been informed that even if a reference does not expressly disclose each limitation, it may still anticipate the claim if any missing element is “inherent,” meaning it is necessarily present or the natural result of the subject matter disclosed.

IV. Obviousness

6. I have been informed by Petitioner’s counsel that, even if a patent claim is not anticipated, it may still be deemed “obvious” if the differences between the claimed subject matter and the prior art would have made it obvious at the time of the invention to a POSA.

7. I have been informed that the obviousness inquiry considers: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) “objective indicia” (sometimes called “secondary considerations”) of nonobviousness.

8. I have also been informed that a POSA provides a reference point from which the prior art and claimed invention should be viewed to prevent using one’s insight or hindsight in deciding whether a claim is obvious. I understand that using the claimed invention as a blueprint to reconstruct the invention from elements in the prior art constitutes hindsight reasoning, which is not permitted.

9. I have been informed that for a claim to be obvious, each element must be disclosed in the prior art. A claim can be shown obvious by combining multiple

references if there is a reason or motivation for a POSA to combine them in the manner claimed, based on knowledge generally available in the art.

10. I have been informed that, in addition to a motivation to combine, persons of skill in the art must have had a reasonable expectation of success in practicing the claimed invention based on the prior art.

11. I have been informed that only analogous art may be considered in an obviousness analysis. Art is analogous if it is within the same field of endeavor as the patent or is reasonably pertinent to the particular problem the patent addresses.

12. I have also been informed that the Board must consider certain “objective indicia” (or secondary considerations), such as commercial success, long-felt but unsolved need, teaching away, unexpected results, copying, and praise by others. These factors support nonobviousness if a relevant nexus exists between the objective factor and the claimed invention.

V. Written Description

13. I have been informed by Petitioner’s counsel that a specification must describe the claimed subject matter in sufficient detail for a POSA to understand it and must show that the inventor actually possessed the invention as claimed. The specification must adequately demonstrate that the inventor had possession of the full scope of the claimed subject matter as of the filing date.

VI. Priority

14. I have been informed by Petitioner's counsel that claims in a continuation or continuation-in-part ("CIP") application (the "child application") are entitled to the benefit of the filing date of the parent application if the parent application's written description sufficiently enables a POSA to practice the invention claimed in the child application.

Appendix C

Claim	Limitations
1	[1pre] A storage stable pharmaceutical product, comprising: [1a] a single use dose vial, and [1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial, [1c] wherein the composition is sterile and lyophilized, and [1d] wherein the composition comprises no less than 98% phenobarbital sodium.
2	[2pre] The pharmaceutical product of claim 1, [2a] wherein the composition has the property that when the composition is stored at 40°C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.
3	[3pre] The pharmaceutical product of claim 1, [3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.
4	[4pre] The pharmaceutical product of claim 1, [4a] wherein the composition has the property that when the composition is stored at 40°C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).
5	[5pre] The pharmaceutical product of claim 1, [5a] wherein the composition is amorphous.

Claim	Limitations
6	[6pre] The pharmaceutical product of claim 1, [6a] wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).
7	[7pre] A pharmaceutical product, comprising: [7a] a single use dose vial, and [7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial, [7c] wherein the composition is sterile and lyophilized, [7d] wherein the composition comprises no less than 98% phenobarbital sodium, and [7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).
8	[8pre] The pharmaceutical product of claim 7, [8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU.
9	[9pre] The pharmaceutical product of claim 7, [9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition

Claim	Limitations
	contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).
10	[10pre] The pharmaceutical product of claim 7, [10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).
11	[11pre] The pharmaceutical product of claim 10, [11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).
12	[12pre] The pharmaceutical product of claim 7, [12a] wherein the composition is amorphous.
13	[13pre] The pharmaceutical product of claim 12, [13a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).
14	[14pre] The pharmaceutical product of claim 1, [14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

Claim	Limitations
15	[15pre] The pharmaceutical product of claim 14, [15a] wherein the composition is amorphous.
16	[16pre] The pharmaceutical product of claim 1, [16a] wherein the product comprises the 100 mg dose in the single use dose vial.
17	[17pre] The pharmaceutical product of claim 7, [17a] wherein the product comprises the 100 mg dose in the single use dose vial.
18	[18pre] The pharmaceutical product of claim 8, [18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).
19	[19pre] The pharmaceutical product of claim 8, [19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).
20	[20pre] The pharmaceutical product of claim 8, [20a] wherein the composition is amorphous.