

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 IPR2025-00893

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

PETITION FOR *INTER PARTES* REVIEW OF
U.S. PAT. NO. 11,878,076

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	GROUND FOR STANDING (37 C.F.R. § 42.104(a))	3
III.	IDENTIFICATION OF CHALLENGE AND STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R. § 42.104(b)).....	3
	A. Prior Art.....	3
	B. Grounds	5
IV.	BACKGROUND OF THE TECHNOLOGY.....	5
	A. Phenobarbital Sodium and its Degradants	5
	B. Strategies for Impurity Control in Pharmaceutical Formulations.....	6
	C. Lyophilization as a Known Technique to Control Impurities	7
	D. Storage Conditions and Stability Testing	7
	E. Final Product Considerations	9
V.	SUMMARY OF THE '076 PATENT AND CHALLENGED CLAIMS	10
VI.	PERSON OF ORDINARY SKILL IN THE ART	12
VII.	CLAIM CONSTRUCTION	13
VIII.	GROUND 1: THE CHALLENGED CLAIMS ARE OBVIOUS OVER PIF, IN VIEW OF PARKER AND WEST-WARD.....	13
	A. PIF	13
	B. Parker.....	14
	C. West-Ward	15
	D. Motivation to Combine Ground 1 References with a Reasonable Expectation of Success.....	15
	E. Claim 1	19

1.	[1pre] A storage stable pharmaceutical product, comprising: ..	19
2.	[1a] a single use dose vial, and.....	20
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, ...	20
4.	[1c] wherein the composition is sterile and lyophilized, and ..	22
5.	[1d] wherein the composition comprises no less than 98% phenobarbital sodium.....	22
F.	Claim 2	23
1.	[2pre] The pharmaceutical product of claim 1,.....	23
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.	23
G.	Claim 3	25
1.	[3pre] The pharmaceutical product of claim 1,.....	25
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.....	25
H.	Claim 4	25
1.	[4pre] The pharmaceutical product of claim 1,.....	25

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).....	26
I.	Claim 5	27
1.	[5pre] The pharmaceutical product of claim 1,.....	27
2.	[5a] wherein the composition is amorphous.	27
J.	Claim 6	28
1.	[6pre] The pharmaceutical product of claim 1,.....	28
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).....	28
K.	Claim 7.....	29
1.	[7pre] A pharmaceutical product, comprising:	29
2.	[7a] a single use dose vial, and.....	29
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, ...	29
4.	[7c] wherein the composition is sterile and lyophilized, ...	29
5.	[7d] wherein the composition comprises no less than 98% phenobarbital sodium, and	30

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).....	30
L.	Claim 8	30
1.	[8pre] The pharmaceutical product of claim 7,.....	30
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.....	30
M.	Claim 9	31
1.	[9pre] The pharmaceutical product of claim 7,.....	31
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 (2EPMMA).	31
N.	Claim 10	31
1.	[10pre] The pharmaceutical product of claim 7,.....	31
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).....	31
O.	Claim 11	32
1.	[11pre] The pharmaceutical product of claim 10,.....	32

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).	32
P.	Claim 12	32
1.	[12pre] The pharmaceutical product of claim 7,.....	32
2.	[12a] wherein the composition is amorphous.	32
Q.	Claim 13	33
1.	[13pre] The pharmaceutical product of claim 12,.....	33
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).....	33
R.	Claim 14	33
1.	[14pre] The pharmaceutical product of claim 1,.....	33
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).....	33
S.	Claim 15	35
1.	[15pre] The pharmaceutical product of claim 14,.....	35
2.	[15a] wherein the composition is amorphous.	35

T.	Claim 16	35
1.	[16pre] The pharmaceutical product of claim 1,.....	35
2.	[16a] wherein the product comprises the 100 mg dose in the single use dose vial.	35
U.	Claim 17	36
1.	[17pre] The pharmaceutical product of claim 7,.....	36
2.	[17a] wherein the product comprises the 100 mg dose in the single use dose vial.	36
V.	Claim 18	36
1.	[18pre] The pharmaceutical product of claim 8,.....	36
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).	37
W.	Claim 19	37
1.	[19pre] The pharmaceutical product of claim 8,.....	37
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).	37
X.	Claim 20	38
1.	[20pre] The pharmaceutical product of claim 8,.....	38
2.	[20a] wherein the composition is amorphous.	38
IX.	GROUND 2: THE CHALLENGED CLAIMS ARE ANTICIPATED BY THE '608 PUBLICATION.....	38

A.	The '076 Patent is Not Entitled to a Priority Date Earlier Than June 30, 2022.....	39
1.	The Original Applications Lack Written Description for the Pharmaceutical Products of the Challenged Claims.....	41
2.	The Original Applications Lack Written Description for Compositions Containing an Organic Solvent.....	42
3.	The Original Applications Lack Written Description for Compositions Having Crystalline Phenobarbital Sodium	44
4.	Patent Owner Cannot Claim Priority for Claims that Include Compositions Not Disclosed in the Original Applications.....	49
B.	Because the Priority Date of the Challenged Claims is June, 30, 2022, they are anticipated by the '608 Publication	53
1.	Claim 1	53
a.	[1pre].....	53
b.	[1a].....	54
c.	[1b].....	54
d.	[1c].....	54
e.	[1d].....	54
2.	Claim 2.....	55
a.	[2pre].....	55
b.	[2a].....	55
3.	Claim 3.....	56
a.	[3pre].....	56
b.	[3a].....	56
4.	Claim 4.....	56
a.	[4pre].....	56

	b.	[4a].....	56
5.		Claim 5.....	57
	a.	[5pre].....	57
	b.	[5a].....	57
6.		Claim 6.....	57
	a.	[6pre].....	57
	b.	[6a].....	57
7.		Claim 7.....	58
	a.	[7pre].....	58
	b.	[7a].....	58
	c.	[7b].....	59
	d.	[7c].....	59
	e.	[7d].....	59
	f.	[7e].....	59
8.		Claim 8.....	59
	a.	[8pre].....	59
	b.	[8a].....	59
9.		Claim 9.....	60
	a.	[9pre].....	60
	b.	[9a].....	60
10.		Claim 10.....	60
	a.	[10pre].....	60
	b.	[10a].....	60

11.	Claim 11	60
	a. [11pre].....	60
	b. [11a].....	60
12.	Claim 12.....	61
	a. [12pre].....	61
	b. [12a].....	61
13.	Claim 13.....	61
	a. [13pre].....	61
	b. [13a].....	61
14.	Claim 14.....	61
	a. [14pre].....	61
	b. [14a].....	61
15.	Claim 15.....	62
	a. [15pre].....	62
	b. [15a].....	62
16.	Claim 16.....	63
	a. [16pre].....	63
	b. [16a].....	63
17.	Claim 17.....	63
	a. [17pre].....	63
	b. [17a].....	63
18.	Claim 18.....	63
	a. [18pre].....	63

b.	[18a].....	64
19.	Claim 19.....	64
a.	[19pre].....	64
b.	[19a].....	64
20.	Claim 20.....	64
a.	[20pre].....	64
b.	[20a].....	64
X.	GROUND 3: THE CHALLENGED CLAIMS ARE OBVIOUS OVER THE '608 PUBLICATION AND THE ORDINARY KNOWLEDGE OF A POSA.....	65
XI.	THERE ARE NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS	68
XII.	TRIAL SHOULD BE INSTITUTED (35 U.S.C. §§ 314(a), 325).....	68
XIII.	CONCLUSION.....	69
XIV.	MANDATORY NOTICES	70
A.	Real Party in Interest (37 C.F.R. § 42.8(b)(1)).....	70
B.	Related Matters (37 C.F.R. § 42.8(b)(2))	70
C.	Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))	70
D.	Service Information (37 C.F.R. § 42.8(b)(4))	71
XV.	PAYMENT OF FEES	71
XVI.	WORD COUNT	72
XVII.	CERTIFICATE OF SERVICE.....	72
	Appendix A	75

TABLE OF AUTHORITIES

Cases

<i>Allen Eng'g Corp. v Bartell Indus., Inc.</i> , 299 F.3d 1336 (Fed. Cir. 2002).....	19
<i>Anascape, Ltd. v. Nintendo of Am., Inc.</i> , 601 F.3d 1333 (Fed. Cir. 2010).....	40
<i>Ariad Pharms., Inc. v. Eli Lilly and Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010).....	39, 41, 42, 44
<i>Arthrex, Inc. v. Smith & Nephew, Inc.</i> , 35 F.4th 1328 (Fed. Cir. 2022)	51
<i>Aventis Pharma Deutschland GmbH v. Lupin, Ltd.</i> , 499 F.3d 1293 (Fed. Cir. 2007).....	66
<i>Bamberg v. Dalvey</i> , 815 F.3d 793 (Fed. Cir. 2016).....	52
<i>Daiichi Sankyo Co., Ltd v. Alethia Biotherapeutics, Inc.</i> , IPR2015-00291, Paper 75 (P.T.A.B. Jun. 14, 2016)	39
<i>Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015).....	39
<i>Fox Factory, Inc. v. SRAM, LLC</i> , 944 F.3d 1366 (Fed. Cir. 2019).....	68
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013).....	21, 35
<i>Gentry Gallery, Inc. v. Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998).....	42, 50
<i>Hamilton Beach Brands, Inc. v. Sunbeam Prods., Inc.</i> , No. 3:11-CV-345, 2012 U.S. Dist. LEXIS 97923 (E.D. Va. July 13, 2012)	40
<i>ICU Med., Inc. v. Alaris Med. Sys.</i> , 558 F.3d 1368 (Fed. Cir. 2009).....	52

<i>In re Curtis</i> , 354 F.3d 1347 (Fed. Cir. 2004).....	42
<i>In re Lukach</i> , 442 F.2d 967 (CCPA 1971).....	39
<i>In re Wilder</i> , 736 F.2d 1516 (Fed. Cir. 1984).....	50
<i>Nivagen, Inc. v. Sun Pharmaceuticals Industries, Inc.</i> , No. 2:24-cv-36-RWS-RSP (E.D. Tex.).....	70
<i>PIN/NIP, Inc. v. Platte Chem. Co.</i> , 304 F.3d 1235 (Fed. Cir. 2002).....	50
<i>PowerOasis, Inc. v. T-Mobile USA, Inc.</i> , 522 F.3d 1299 (Fed. Cir. 2008).....	40
<i>Research Corp. Techs., Inc. v. Microsoft Corp.</i> , 627 F.3d 859 (Fed. Cir. 2010).....	41, 52
<i>Sanofi-Aventis Deutschland GMBH v. Mylan Pharms. Inc.</i> , Nos. 2020-2066, 2020-2068, 2020-2069, 2021 U.S. App. LEXIS 38482 (Fed. Cir. Dec. 29, 2021)	39
<i>Spectrum Pharms., Inc. v. Sandoz Inc.</i> , 802 F.3d 1326 (Fed. Cir. 2015).....	66
<i>Tronzo v. Biomet</i> , 156 F.3d 1154 (Fed. Cir. 1998).....	47, 50
<i>Trs. of Bos. Univ. v. Everlight Elecs. Co.</i> , 896 F.3d 1357 (Fed. Cir. 2018).....	39
Statutes	
35 U.S.C. § 102	passim
35 U.S.C. § 112	39, 40, 50
35 U.S.C. § 120	39
35 U.S.C. § 314	68

35 U.S.C. § 325	68
-----------------------	----

35 U.S.C. §103	3
----------------------	---

Other Authorities

MPEP § 2163	50
-------------------	----

Regulations

37 C.F.R. § 42.10	71
-------------------------	----

37 C.F.R. § 42.103	71
--------------------------	----

37 C.F.R. § 42.104	3
--------------------------	---

37 C.F.R. § 42.105	72
--------------------------	----

37 C.F.R. § 42.15	71
-------------------------	----

37 C.F.R. § 42.24	71
-------------------------	----

37 C.F.R. § 42.6	72
------------------------	----

37 C.F.R. § 42.8	70, 71
------------------------	--------

LIST OF EXHIBITS

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	ICH Topic Q1A Stability Testing Guidelines: <i>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

I. INTRODUCTION

Sun Pharmaceutical Industries, Inc. (“Petitioner”) petitions for *inter partes* review of claims 1–20 of U.S. Patent No. 11,878,076 (“the ’076 Patent”) (Ex-1001), assigned to Nivagen Pharmaceuticals, Inc. (“Patent Owner”). Claims 1–20 (the “challenged claims”) cover pharmaceutical products comprising lyophilized phenobarbital sodium compositions in specific dosage amounts with high purity and low levels of specific impurities.

According to the specification, the alleged invention is based on the “surprising” discovery that lyophilizing phenobarbital sodium results in a formulation that is more stable and resistant to degradation than known non-lyophilized phenobarbital sodium compounds. Ex-1001 at 2:4–24; 2:53–67. There are two problems with this alleged discovery that negate the patentability of the challenged claims.

One: lyophilization (removing water through freeze-drying) was a well-known way to increase stability and reduce the degradation of compounds that, like phenobarbital sodium, were known to degrade in the presence of water. Even more, a company in Japan named Nobelpharma had publications describing its commercially available lyophilized phenobarbital sodium product long before 2019, the earliest possible priority date for the ’076 patent. Ground 1 relies on a prior art printed publication relating to Nobelpharma’s commercial product

“Nobelbar” called the Pharmaceutical Interview Form (Ex-1008, “PIF”). As explained below, all of the challenged claims would have been obvious over PIF in view of Parker (Ex-1012) and West-Ward (Ex-1013).

Two: the claims of the '076 patent are not entitled to the priority date of either Application No. 17/025,881 (the “'881 application”) or provisional application No. 62/903,511 (the “'511 application”) (collectively, the “Original Applications”). The inventions contemplated by and disclosed in the Original Applications were intentionally and expressly limited to *amorphous* phenobarbital sodium compositions that *excluded* organic solvents because those features allegedly conferred unexpected stability and better safety, respectively.

It was not until after Patent Owner learned of Petitioner’s interest in phenobarbital sodium products that Patent Owner filed a continuation-in-part application, No. 17/854,914 (the “'914 CIP application”, Ex-1007), and sought to expand its patent coverage. The '914 CIP application included over 14 pages of additional disclosure that, for the first time, disclosed *non-amorphous* phenobarbital sodium compositions *containing* organic solvents. By adding substantial new matter and broadening the claims, Patent Owner eliminated the very features that had allegedly conferred benefits to the originally disclosed compositions.

As a result, the earliest priority date that the challenged claims are entitled to is the June 30, 2022, filing date of the '914 CIP application. In the meantime, the '881 application published as U.S. Publication No. US2021/0085608 (the "'608 Publication", Ex-1005) on March 25, 2021—more than one year prior to the filing of the '914 CIP. While the '608 Publication does not provide adequate written description support for the full scope of the challenged claims, it nonetheless discloses compositions that fall within the scope of those claims. Therefore, as explained below in connection with Grounds 2 and 3, the challenged claims are anticipated and/or rendered obvious by the '608 Publication.

Because the challenged claims are unpatentable under 35 U.S.C. §§ 102 and 103, Petitioner respectfully requests that trial be instituted.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '076 Patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting such review on the identified Grounds.

III. IDENTIFICATION OF CHALLENGE AND STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R. § 42.104(b))

A. Prior Art

The '076 Patent, filed on January 24, 2023, claims priority to the '914 CIP application, which was filed on June 30, 2022. The '914 CIP application claims priority to the Original Applications, the earliest of which was filed on September

20, 2019. Thus, the earliest possible priority date for the '076 patent is September 20, 2019. However, as explained in detail below, because the claims encompass new matter first introduced in the '914 CIP application, the '076 patent is entitled to a priority date no earlier than June 30, 2022. Each reference below was filed or publicly available before even the earliest possible priority date of September 20, 2019, except for the '608 Publication, which published before the actual priority date for the '076 patent claims of June 30, 2022.

PIF (Ex-1009)¹, published by 2011, is prior art under post-AIA §102(a), because it was made available to the public at least by posting publicly online in a location where an interested POSA exercising reasonable diligence could locate it. Ex-1015 ¶¶89–92; Ex-1011 (demonstrating public availability by March 2011). Because a POSA would have known about the phenobarbital sodium products on the market as a matter of routine study, including Nobelbar, they would have reviewed the Nobelpharma website to learn more about the product and naturally located and reviewed the PIF to gain further insight. Ex-1015 ¶¶89–92.

¹ Ex-1009 is a certified English-language translation of the original foreign-language PIF publication (Ex-1008). Ex-1010 (translator certification attesting to accuracy of the translation). For ease of reference, the translated Ex-1009 is cited throughout to refer to the original PIF publication.

Parker (Ex-1012), published on May 25, 2017, is prior art under post-AIA § 102(a). Ex-1015 ¶93.

West-Ward (Ex-1013), published by 2015, is prior art under post-AIA § 102(a), because it was made available to the public at least by posting publicly online in a location where an interested POSA exercising reasonable diligence could locate it. Ex-1015 ¶94; Ex-1014 (demonstrating public availability by October 2015).

'608 Publication (Ex-1005), published on March 25, 2021, is prior art under post-AIA § 102(a).

B. Grounds

Ground		Claims	Prior Art
1	Section 103	1–20	PIF (Ex-1009) Parker (Ex-1012) West-Ward (Ex-1013)
2	Section 102	1–20	'608 Publication (Ex-1005)
3	Section 103	1–20	'608 Publication (Ex-1005)

This Petition is also supported by the Declaration of Raj Suryanarayanan, Ph.D., as an expert in the field of the '076 patent. Ex-1015 ¶¶1–17.

IV. BACKGROUND OF THE TECHNOLOGY

A. Phenobarbital Sodium and its Degradants

As of 2019, phenobarbital sodium was a well-established compound in the field of pharmaceutical sciences, widely recognized for its anticonvulsant,

hypnotic, and sedative properties. Ex-1009 at 1, 4, 42–43; Ex-1015 ¶¶59–61. It was known to be susceptible to hydrolytic degradation. Ex-1017 at 7; *see also id.* at 10–11; Ex-1009 at 7; Ex-1005 at Abstract, [0006] – [0007], [0017], [0023], [0073]; Ex-1015 ¶61.

It was further understood, as of 2019, that the degradation of phenobarbital sodium in the presence of water leads to the formation of toxic impurities. Ex-1012 at [0004], [0030]. Hydrolysis of the phenobarbital ring structure produces harmful degradation products, such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). Ex-1012 at [0004], [0006], [0007], Table 1; Ex-1015 ¶61; *see also* Ex-1009 at 12.

Degradation, and the resulting formation of toxic impurities, was known to be further accelerated by conditions such as basic reactions, oxidation, and heat. Ex-1012 at [0007]; Ex-1015 ¶61.

B. Strategies for Impurity Control in Pharmaceutical Formulations

The pharmaceutical industry has long focused on improving formulation stability in an effort to minimize impurities. Ex-1018 at 1–2; Ex-1015 ¶¶62–70.

“[D]eveloping procedures to minimize key impurities in a drug substance is generally straightforward” once their structures are known. Ex-1022 at 280; Ex-1015 ¶69. Controlling impurities in APIs is critical to ensure safety, as failure to do

so can result in significant safety, moral, and economic impacts. Ex-1023 at 390; Ex-1018 at 3-4; Ex-1015 ¶¶66–70.

C. Lyophilization as a Known Technique to Control Impurities

Lyophilization, or freeze-drying, is a dehydration process commonly used to enhance stability of pharmaceutical products. *See, e.g.*, Ex-1021 at 17; Ex-1024 at 5; Ex-1015 ¶¶71–76; *see also* Ex-1026 at 54; Ex-1027 at 18, 257, 466. The lyophilization process involves the steps of freezing, sublimation, and then gradual heating to remove any remaining bound water. *See, e.g.*, Ex-1021 at 17; Ex-1024 at 5; Ex-1015 ¶¶71–74, 76; *see also* Ex-1026 at 54; Ex-1027 at 18, 257, 466.

Lyophilization reduces moisture to low levels, minimizing moisture-based degradation and ensuring drug product stability and extended shelf life. *See, e.g.*, Ex-1021 at 17; Ex-1024 at 2; Ex-1025 at 20; Ex-1015 ¶¶71, 74, 76. Removing water without excessive heat also maintains the structural integrity and biological activity of sensitive compounds. Ex-1021 at 17; Ex-1024 at 1–2; Ex-1025 at 20; Ex-1015 ¶¶71, 73. Lyophilization further ensures microbial sterility, as the solution is sterile-filtered before final packaging, significantly minimizing contamination risks. Ex-1026 at 54–55; Ex-1015 ¶¶72, 74.

D. Storage Conditions and Stability Testing

Stability testing is typically conducted under standardized conditions, including specific temperature, relative humidity, and time parameters, to provide

reliable data on the product's shelf life and the likely degradation products. Ex-1035 at 2, 4; Ex-1036 at 5–6; Ex-1015 ¶77.

Long-term, intermediate, and accelerated storage conditions for finished products are well known:

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 Table 2.2.7.1; *see also* Ex-1035 at 4, 7; Ex-1036 at 7–10, 12–17; Ex-1015 ¶78.

Testing in long-term studies must be conducted at intervals sufficient to establish the stability profile. Ex-1034 at 7, 16; Ex-1035 at 4, 8; Ex-1036 at 7, 12; Ex-1015 ¶79. For products with a proposed shelf life of 12 months or more, testing is typically conducted every three months in year one, every six months in year two, and annually thereafter. *Id.* For lyophilized products, routine stability evaluations require reconstitution with enough water to fully dissolve the drug product, which is necessary to ensure reliable assessments. Ex-1015 ¶80. It would be routine for a POSA to use a round-number volume, such as 10 mL, in the

reconstitution of the drug product for purposes of stability testing. *Id.*; Ex-1037 at 1-4, 9; Ex-1038 at 2; Ex-1039 at 2:39-50, 5:21-25, 5:31-34; *id.* at passim.

These standardized conditions ensure that the product maintains its intended quality throughout its shelf life. Ex-1034 at 5, 7, 13-14, 16-18; *see also* Ex-1035 at 4-5, 8-9; Ex-1036 at 5; Ex-1015 ¶¶77, 82-83. Stability after reconstitution or dilution must be evaluated under these standardized conditions to provide comprehensive data that supports labeling and storage instructions. Ex-1035 at 7-9; Ex-1015 ¶¶77-83.

E. Final Product Considerations

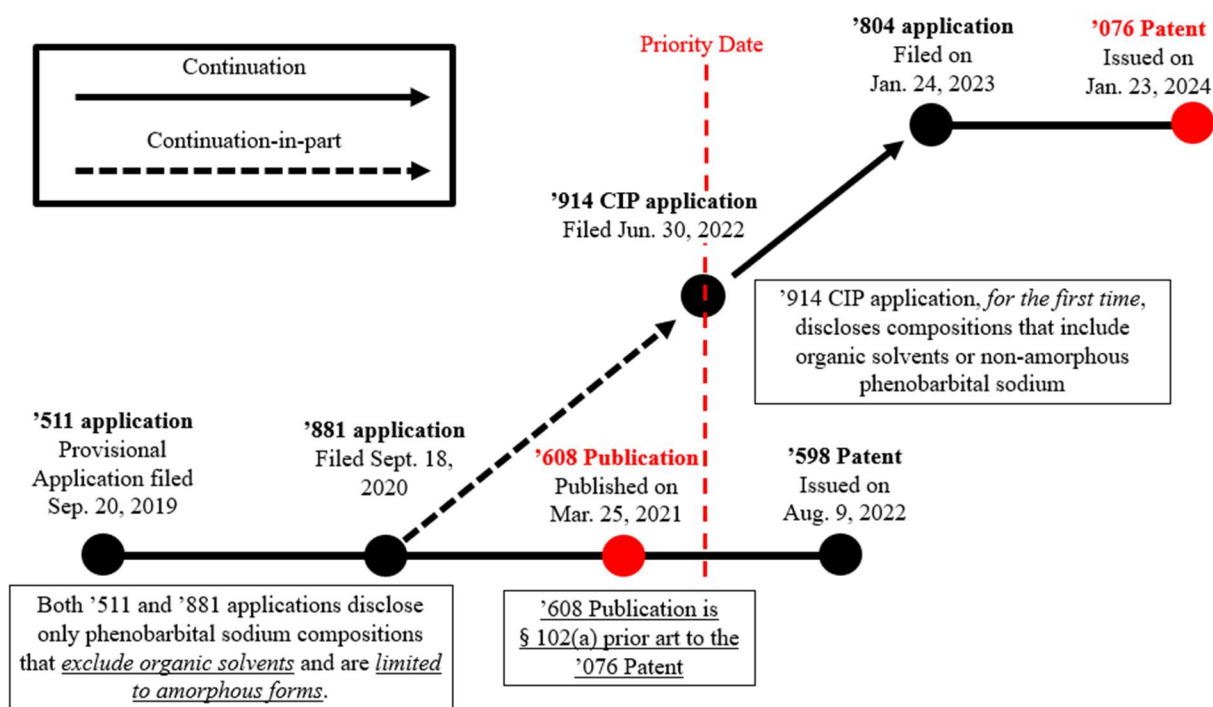
The pharmaceutical industry has long appreciated the criticality of sterility for injectable products, including lyophilized products. *See, e.g.*, Ex-1021 at 8, 13, 26; Ex-1015 ¶64. Sterility is required for all parenteral products, regardless of the formulation. Ex-1015 ¶64.

Injectable products pose a risk of spreading infection in healthcare settings, making single-use vials preferable over multiple-dose vials. Ex-1019 at 45; Ex-1015 ¶63. Unlike single-use formulations, multiple-dose formulations typically contain antimicrobial preservatives to prevent contamination. Ex-1020 at 6-7; Ex-1015 ¶63.

V. SUMMARY OF THE '076 PATENT AND CHALLENGED CLAIMS

The '076 Patent, entitled “Lyophilized compositions of phenobarbital sodium salt,” issued from the '804 application filed on January 24, 2023. Ex-1015 ¶¶19–20. The '076 Patent on its face lists the following related application data: the '914 CIP application filed on June 30, 2022; the '881 application filed on September 18, 2020; and the '511 application, which is a provisional application filed on September 20, 2019.

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



Ex-1015 ¶21.

The Original Applications disclosed lyophilized formulations of phenobarbital sodium that were (1) free of organic solvents; and (2) amorphous. Patent Owner stated in the Original Applications that its disclosed formulations

excluded organic solvents because they are “not desirable in general and indeed not suitable for administration to newborns as described in the art.” Ex-1003 at 7 (¶[0007]); Ex-1004 at 195 (¶[0008]). Patent Owner further explained that the compositions of its alleged invention were amorphous and theorized that the amorphous nature of the compositions led to enhanced stability. Ex-1004 at 643; *see also id.* at 636, 196 (¶[0011]). The Original Applications published as US 2021/0085608 (“the ’608 Publication”) on March 25, 2021, and issued as U.S. Patent No. 11,406,598 on August 9, 2022.

On June 30, 2022, Patent Owner filed the ’914 CIP application. Despite the fact that the Original Applications were directed to lyophilized formulations that were explicitly free of organic solvents and amorphous, the ’914 CIP Application included claims directed to compositions that were broad enough to encompass both compositions containing organic solvents and compositions that were crystalline. To support these new, broader claims, Patent Owner added substantial new matter to the ’914 CIP application, including roughly 30 columns and 16 tables of information. Some of the new matter included in the ’914 CIP application was from experiments conducted by Patent Owner prior to the filing of the Original Applications, but that Patent Owner *deliberately did not include or disclose* in the Original Applications. Ex-1001 at Table 31, 32. Exhibit 1050 highlights the new matter that was added in the ’914 CIP application.

The '914 CIP application issued as the '076 patent on January 23, 2024.

Claims 1–20 of the '076 patent are the challenged claims in this Petition and reproduced in **Appendix A**, divided into limitations to guide the analysis.

The challenged claims 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; cls. 1–20; Ex-1015 ¶¶22–58. Specifically, the challenged claims of the '076 Patent are directed to lyophilized phenobarbital sodium compositions that contain minimal amounts of the degradation products PEAU, 2EPMM, and PBG. Ex-1001 at cls. 2–20.

VI. PERSON OF ORDINARY SKILL IN THE ART

A POSA for the '076 Patent would have at least 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 reconstituted pharmaceutical compositions. A POSA would also understand that the process of drug product development involves a multidisciplinary approach and would have had access to and would have consulted with a collaborative team of ordinarily skilled scientists having specialized skills in various aspects of drug development to solve problems that may arise. Ex-1015 ¶¶16–17.

VII. CLAIM CONSTRUCTION

Petitioner does not believe any claim terms require specific construction for the purpose of deciding the Grounds 1–3 challenges set forth in this Petition.²

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

The challenged claims were obvious as of September 20, 2019—the filing date of the earliest application to which the '076 patent claims priority, the '511 application—based on PIF, in view of Parker and West-Ward, along with the knowledge of a POSA. Ex-1015 ¶¶88–192.

A. PIF

PIF is a “pharmaceutical interview form” for Nobelbar, which is a document published in Japan as a supplement to the package insert for Nobelbar.³ PIF teaches

² Petitioner reserves the right to address claim construction issues in the federal court litigation. For example, Petitioner may contend in the district court case that Patent Owner disclaimed compositions containing organic solvents in the specification. However, Patent Owner will dispute that contention and, accordingly, Petitioner agrees to apply the broader plain and ordinary meaning in this proceeding.

³ Nobelbar is a commercial product that has been approved for use in Japan since 2008. Ex-1015 ¶97; Ex-1009 at 1.

a lyophilized drug containing 274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial for intravenous injection. Ex-1009 at 1, 7, 38; Ex-1015 ¶¶97. PIF teaches a lyophilized injection composed of phenobarbital sodium only, without additives. Ex-1009 at 4, 7; Ex-1015 ¶¶97. A POSA researching phenobarbital sodium compositions would naturally familiarize themselves with publications describing such compositions and would have been aware of the published PIF supplement to the package insert. Ex-1015 ¶¶89–90. The PIF was designed to provide material information about a drug that “supplements information in the package inserts.” Ex-1009 at 2. A POSA would have reviewed publicly available technical information relating to Nobelbar and would have reviewed various Nobelbar regulatory documents, including PIF.

B. Parker

U.S. Patent Application Publication No. US 2017/0143719 (“Parker”) discloses a “stable formulation of phenobarbital sodium injection” that minimizes impurity formation during extended storage. Ex-1012 at Title, Abstract, [0002], [0016]–[0017], [0023], [0029], [0036]; Ex-1015 ¶102. Parker explains that traditional phenobarbital sodium formulations, which are typically dissolved in water, undergo hydrolysis, leading to the destruction of the phenobarbital ring complex and the formation of toxic impurities such as PEAU, 2EPMM, and PBG. Ex-1012 at Title, Abstract, [0004], [0006], [0016]–[0017], [0036], [0039], Table 1,

cl. 1; Ex-1015 ¶102. A POSA researching phenobarbital sodium would have familiarized themselves with patents relating to phenobarbital sodium, including those like Parker that discuss degradation. Ex-1012 at [0017]; Ex-1015 ¶¶93, 102.

C. West-Ward

West-Ward is a page from the NIH’s “DailyMed” website detailing drug label information for a phenobarbital sodium injection product sold by West-Ward. West-Ward discloses commercially available products of “Phenobarbital Sodium Injection, USP,” sold in dosages of 65 mg/mL and 130 mg/mL in a 1 mL vial. Ex-1013. A POSA looking to develop a phenobarbital sodium product would have familiarized themselves with commercially available phenobarbital sodium products and thus would have been aware of the product that had been sold for decades by West-Ward Pharmaceutical Corp. Ex-1015 ¶94. A POSA would have looked to reliable sources for information relating to that product, including the NIH’s “DailyMed” website page relating to the West-Ward product. Ex-1015 ¶94.

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

A POSA would have been motivated in 2019 to develop a stable, lyophilized, highly pure phenobarbital sodium composition given that it was known that phenobarbital sodium was an effective drug to treat seizures, and degraded via hydrolysis into harmful impurities. Ex-1015 ¶105. Lyophilizing phenobarbital sodium would have been an obvious technique at the time to

increase its stability, minimize harmful impurities, and ensure that it could be quickly reconstituted for prompt use. Ex-1015 ¶¶71–76, 105. A POSA would have known, in fact, that it had already been done and was commercially available in Japan. Ex-1015 ¶106.

More specifically, a POSA in 2019 would have known and naturally combined PIF, Parker, and West-Ward to make a shelf-stable, highly-pure, sterile, lyophilized, amorphous phenobarbital sodium composition having minimal impurities, including PEAU, 2EPMM, and PBG, in a single use vial in various dosage amounts, including 65 mg, 100 mg, 135 mg, and 200 mg. Ex-1015 ¶¶104–16.

Reviewing the PIF, a POSA would have recognized the feasibility of a shelf-stable, sterile, and lyophilized phenobarbital sodium product, such as Nobelbar, with high purity and no additives in a single-use vial. Ex-1009 at 4, 7, 21–22, 38; Ex-1015 ¶¶97–101, 106; *supra* Sections IV.C, IV.E. A POSA would have also understood from PIF that Nobelbar had been approved and was commercially available in Japan for over a decade at the time of Patent Owner’s alleged invention. Ex-1015 ¶¶89–92, 97–101, 106; *supra* Section IV.C. Since phenobarbital sodium is typically administered intravenously or intramuscularly, a POSA would have been motivated to maximize purity, increase stability, and minimize impurities, particularly when the compositions are intended for neonatal use. Ex-

1009 at 4, 13, 38, 42; Ex-1015 ¶¶97, 100, 105–06, 109–10; *supra* Section IV.B; *see also Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301–02 (Fed. Cir. 2007); *Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1334–35 (Fed. Cir. 2015). Nobelbar, approved in Japan for the treatment of neonatal convulsions, underscores the need for highly pure formulations, especially for vulnerable pediatric populations who are more sensitive to impurities in drug products. Ex-1009 at 4, 13, 38, 42; Ex-1015 ¶¶97, 100, 106, 109–10.

Parker teaches that phenobarbital sodium is susceptible to hydrolysis and may degrade into harmful impurities, including PEAU, 2EPMM, and PBG. Ex-1012 at [0004], [0006], [0007], Table 1; *supra* Section IV.A. A POSA would have been motivated to identify, screen, control, and, if needed, reduce the formation of toxic degradants to make a more stable and safer product. Ex-1009 at 7; Ex-1012 at [0004], [0006], [0007], Table 1; Ex-1015 ¶¶62–70, 105, 109–11; *supra* Section IV.B. A POSA would have readily recognized that PIF’s use of lyophilization would have reduced impurities that resulted from hydrolysis as described by Parker. Ex-1015 ¶¶71–76, 105, 110, 115; *supra* Section IV.C. The POSA would have further monitored the presence of impurities, particularly PEAU, 2EPMM, and PBG, using well-known stability testing and storage conditions, including storage at 40°C for 6 months under accelerated conditions or at room temperature

for 6 and 24 months after reconstituting the lyophilized drug product in 10 mL of aqueous solution. Ex-1015 ¶¶77–83, 105, 107–08, 110; *supra* Section IV.D.

A POSA would have also been motivated to combine the teachings of PIF and Parker with West-Ward, as West-Ward discloses phenobarbital sodium compositions in known dosage amounts of 65 mg/mL and 130 mg/mL. Ex-1013; Ex-1015 ¶112. A POSA would have further understood that a vial containing 65 mg phenobarbital sodium corresponds to a single dose for a neonate weighing approximately 3.25 kg (7 pounds), and a vial containing 130 mg corresponds to a single dose for an infant weighing around 6.5 kg (14 pounds). Ex-1015 ¶125. A POSA would have been motivated to combine the known dosage amounts of West-Ward with the teachings of Parker, which discloses phenobarbital sodium formulations in amounts of 15-200 mg/mL. Ex-1012 at Abstract, [0017], [0031]; Ex-1015 ¶124.

In addition, a POSA would understand that any lyophilized phenobarbital sodium product must meet safety and regulatory requirements. Ex-1015 ¶111. A POSA would already know and understand that injectable dosage forms must be sterile and thus would have been motivated to ensure sterility for any phenobarbital sodium product. Ex-1015 ¶¶105, 111, 113.

A POSA would have readily combined the teachings from PIF, Parker, and West-Ward. Each challenged claim, divided into limitations as reflected in Appendix A, is discussed below.

E. Claim 1

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

The preamble generally does not constitute a limitation and therefore does not limit the claims. *Allen Eng'g Corp. v Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). To the extent the preamble is considered limiting,⁴ PIF discloses this element. PIF discloses Nobelbar, a lyophilized phenobarbital sodium drug product approved in Japan for intravenous injection. Ex-1009 at 1, 4, 13, 38, 42. It also discloses stability studies of Nobelbar showing it is storage stable, with no changes in the drug substance's and drug formulation's properties over long-term storage tests and accelerated tests. Ex-1009 at 6–7; *see also* Ex-1009 at 38 (reporting Nobelbar has a 3-year shelf life).

A POSA would have recognized the viability and effectiveness of lyophilized phenobarbital sodium based on PIF and would have been motivated to

⁴ Throughout this petition, Petitioner addresses the preambles of the '076 Patent claims only to the extent Patent Owner tries to claim they are limiting.

provide a storage-stable lyophilized phenobarbital sodium composition. Ex-1015 ¶¶117–19.

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

PIF discloses this element. PIF teaches that Nobelbar contains 274 mg of phenobarbital sodium per vial (equivalent to 250 mg of phenobarbital) without additives. Ex-1009 at 1, 4, 7, 38. PIF further details that the approved dosage of Nobelbar for neonatal convulsions is an initial dose of 20 mg/kg intravenously, with additional doses as needed (not exceeding the initial dose), and a maintenance dose of 2.5–5 mg/kg daily, and for status epilepticus, the dosage is 15–20 mg/kg daily. Ex-1009 at 13, 42. PIF discloses that after dissolution, Nobelbar should be used promptly within 6 hours. Ex-1009 at 7–8, 34. A POSA would have known that a vial of the Nobelbar product described in PIF was for single-use dosing to align with the recommended intravenous administration protocols. Ex-1015 ¶¶120–23. Furthermore, because the Nobelbar formulation does not include any additives, including antimicrobial preservatives, a POSA would have understood that a Nobelbar dosage vial is for single-use. Ex-1015 ¶¶63, 120; *supra* Section IV.E.

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,

PIF, West-Ward, and Parker each disclose doses of phenobarbital sodium. A POSA developing a lyophilized phenobarbital sodium product, like the Nobelbar

product disclosed in PIF, would need to select appropriate dosage amounts. West-Ward teaches that phenobarbital sodium injections were commercially available in concentrations of 65 mg/mL and 130 mg/mL, while Parker discloses dosage amounts between 15 and 200 mg/mL. Ex-1013; Ex-1012 at Abstract, [0017], [0031]. PIF also discloses the commercial availability of 30 mg, 50 mg, 60 mg, and 130 mg per 1 mL phenobarbital sodium injection products in the United States. Ex-1009 at 42. A POSA would have understood that selecting or modifying dosage amounts, such as those disclosed in West-Ward, Parker, and PIF, to achieve expected therapeutic outcomes is a routine modification within the skill in the art and does not require inventive steps. Ex-1015 ¶¶124–26; *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736–39 (Fed. Cir. 2013).

A POSA would have further understood that a vial containing 65 mg phenobarbital sodium corresponds to a single dose for a neonate weighing approximately 3.25 kg (7 pounds), and a vial containing 130 mg corresponds to a single dose for an infant weighing around 6.5 kg (14 pounds). Ex-1015 ¶125. A POSA would have been motivated with a reasonable expectation of success to use these well-accepted dosages, knowing they minimize risks and uncertainties in formulation development, given their established efficacy and safety profiles. *Id.*

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

PIF discloses that Nobelbar was a lyophilized drug product. Ex-1009 at 1, 4, 7. PIF explains that Nobelbar was an intravenous drug product, so a POSA would know it was sterile. *Id.* at 1, 4, 7, 13; Ex-1015 ¶127; *Supra* Section IV.C. The stability studies and rigorous testing detailed in PIF, including microbial limits and precise moisture control during lyophilization, confirm that Nobelbar and similar lyophilized products are sterile and free from particulates. Ex-1009 at 6–7; Ex-1015 ¶128. A POSA would further have understood that sterility is required for any injectable drug product and would possess the knowledge required to ensure sterility in the final drug product. Ex-1015 ¶129. Thus, a POSA would have been motivated, with a reasonable expectation of success, to have the phenobarbital sodium composition be sterile and lyophilized, like the Nobelbar product disclosed by PIF. Ex-1015 ¶¶127–30.

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

PIF describes Nobelbar as a lyophilized injection composed of drug substance only, without additives. Ex-1009 at 4, 7; Ex-1015 ¶¶97, 131. A POSA would know that a composition without additives, particularly for intravenous administration to neonates, would be of high-purity, approaching, meeting or exceeding a threshold of 98% phenobarbital sodium. Ex-1015 ¶¶131–32. The practicality, stability, and safety of the compositions disclosed in PIF highlight the

benefits of high-purity formulations, motivating a POSA to pursue this approach with a reasonable expectation of success. Ex-1015 ¶133. As a matter of routine, a POSA would have known how to, and been motivated to, modulate secondary drying parameters during lyophilization to further reduce moisture and residual solvent content. Ex-1027 at 466.

F. Claim 2

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–35; *supra* Section VIII.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.

PIF discloses that phenobarbital sodium is “[e]xtremely soluble in water” and “hygroscopic,” gradually decomposing when exposed to moist air. Ex-1015 ¶136; Ex-1009 at 7. Parker also teaches that hydroxyl ions from water in phenobarbital sodium formulations “result[] in a hydrolysis pathway that can destroy the phenobarbital ring complex,” forming “harmful” degradation products such as PEAU, 2EPMM, and PBG. Ex-1015 ¶137; Ex-1012 at [0004], [0006], [0007], Table 1; *see also id.* at Title, Abstract, [0017], [0030], [0036], [0039], cl. 1. PIF similarly notes that certain related substances, such as PEAU, may be

generated during manufacturing. Ex-1015 ¶137; Ex-1009 at 12. Parker discloses that these degradation processes are exacerbated by conditions such as reactions with bases, oxidation, and exposure to heat. Ex-1015 ¶137; Ex-1012 at [0007]. A POSA would aim to control impurities by minimizing water and other reactive substances to ensure the stability and safety of phenobarbital sodium formulations, especially for injectable forms where purity is important. Ex-1015 ¶¶138–39.

A POSA would know that lyophilization would reduce hydrolysis and therefore minimize degradation impurities. Ex-1015 ¶61; Ex-1012 at [0004], [0006], [0007], Table 1; *supra* Section IV.A. PIF teaches that Nobelbar reported no changes in stability (other than moisture content) when evaluated using standard and well-known long-term storage tests ($25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$ (at room temperature), in the dark, 36 months) and accelerated tests ($40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$, in the dark, 6 months). Ex-1009 at 6–8; Ex-1015 ¶¶77–83, 140; *supra* Section IV.D. A POSA would have monitored harmful degradants, including PEAU, using the same standard storage test conditions. Ex-1015 ¶¶140–41. Specifically, a POSA would have used standard testing conditions, including storing the composition at 40°C for six months, reconstituting in 10 mL of water, and evaluating impurities like PEAU. Ex-1015 ¶¶77–83, 140–41; *supra* Section IV.D.

Based on the documented success of stable formulations like Nobelbar described in PIF, a POSA would expect to successfully minimize PEAU to very

low levels and certainly no more than 0.1% in a lyophilized phenobarbital sodium composition reconstituted for injection with 10 mL of water after being stored at 40°C for 6 months. Ex-1015 ¶¶136–42.

G. Claim 3

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–34, 143; *supra* Section VIII.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.

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 144, 176–78; *see infra* Section VIII.R.2.

H. Claim 4

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–34, 145; *supra* Section VIII.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).**

As described above with respect to Element [2a], Parker teaches that phenobarbital sodium can degrade into harmful impurities such as 2EPMM and PBG. Ex-1015 ¶¶136–42, 146–47; *supra* Section VIII.F.2. A POSA would aim to reduce impurities by removing water and reactive substances, using lyophilization to minimize hydrolysis and impurities. Ex-1015 ¶¶59–61, 71–76, 136–42, 146–47; *supra* Sections IV.A, IV.C, VIII.F.2. PIF demonstrates Nobelbar’s stability under standard accelerated tests, providing a framework for monitoring degradants like 2EPMM and PBG. Ex-1015 ¶¶140–41, 146–47; *supra* Section VIII.F.2. Specifically, a POSA would have used standard testing conditions, including storing the composition at 40°C for six months, reconstituting in 10 mL of water, and evaluating impurities like 2EPMM and PBG. Ex-1015 ¶¶77–83, 140–41, 146–47; *supra* Section IV.D.

Based on Nobelbar’s documented stability, a POSA would expect to minimize 2EPMM and/or PBG to very low levels and certainly no more than 0.05% 2EPMM and/or PBG in a lyophilized phenobarbital sodium composition reconstituted for

injection with 10 mL of water after being stored at 40°C for 6 months. Ex-1015 ¶¶136–42, 146–47; *supra* Section VIII.F.2.

I. Claim 5

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]–[1d]. Ex-1015 ¶¶117–34, 148; *supra* Section VIII.E.

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

PIF discloses Nobelbar, Japan’s approved lyophilized phenobarbital drug for intravenous injection. Ex-1009 at 1, 4, 13. A POSA would have known that rapid freezing during the lyophilization process converts materials to amorphous forms and would have expected that routine lyophilization techniques would result in the formation of amorphous phenobarbital sodium. Ex-1015 ¶¶75, 149; *supra* Section IV.C.

Further, a POSA would be motivated to create an amorphous product because amorphous lyophilized products have shorter reconstitution time compared to crystalline lyophilized products, and rapid reconstitution is critical when treating an infant or neonate for seizures. Ex-1015 ¶¶150–51.

J. Claim 6

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–34, 152; *supra* Section VIII.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).

As described in Element [2a], Parker teaches that phenobarbital sodium can degrade into harmful impurities like PEAU. Ex-1015 ¶¶136–42, 153, 155; *supra* Section VIII.F.2. PIF demonstrates Nobelbar’s stability under standard long-term storage conditions, including 36 months at room temperature, providing a framework for monitoring degradants like PEAU. Ex-1015 ¶¶140–41, 153–54; *supra* Section VIII.F.2. Specifically, a POSA would have used standard testing conditions, including storing the composition at room temperature for 24 months, reconstituting in 10 mL of water, evaluating impurities like PEAU, and reasonably expected to obtain very low levels of PEAU and certainly at most 0.1% after reconstitution. Ex-1015 ¶¶77–83, 140–41, 153–55; *supra* Section IV.D.

Based on Nobelbar’s documented stability, a POSA would expect to minimize PEAU to very low levels and certainly no more than 0.1% PEAU in a lyophilized phenobarbital sodium composition reconstituted for injection with 10

mL of water after being stored at room temperature for 24 months. Ex-1015

¶¶136–42, 153–55; *supra* Section VIII.F.2.

K. Claim 7

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

PIF discloses Nobelbar, which is a pharmaceutical product. Ex-1015 ¶¶117–19, 156–57; *supra* Section VIII.E.1.

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

As described in Element [1a], PIF disclosed and would have rendered obvious this element. Ex-1015 ¶¶120–23, 158; *supra* Section VIII.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,

As described in Element [1b], PIF in view of Parker and West-Ward would have disclosed and rendered obvious this element. Ex-1015 ¶¶124–26, 159; *supra* Section VIII.E.3.

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

As described in Element [1c], PIF disclosed and rendered obvious this element. Ex-1015 ¶¶127–30, 160; *supra* Section VIII.E.4.

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

As described in Element [1d], PIF disclosed and would have rendered obvious this element. Ex-1015 ¶¶131–33, 161; *supra* Section VIII.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).**

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 162, 176–78; *infra* Section VIII.R.2.

L. Claim 8

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. Ex-1015 ¶¶117–34, 156–63; *supra* Section VIII.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.**

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 164, 176–78; *infra* Section VIII.R.2.

M. Claim 9

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

PIF in view of West-Ward and Parker discloses and renders obvious limitations of [7pre]-[7e]. Ex-1015 ¶¶117–34, 156–62, 165; *supra* Section VIII.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 (2EPM).

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 166, 176–78; *infra* Section VIII.R.2.

N. Claim 10

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

PIF in view of West-Ward and Parker discloses and renders obvious limitations of [7pre]-[7e]. Ex-1015 ¶¶117–34, 156–62, 167; *supra* Section VIII.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).

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 168, 176–78; *infra* Section VIII.R.2.

O. Claim 11

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

PIF in view of West-Ward and Parker discloses the pharmaceutical product that teaches limitations of [10pre]-[10a]. Ex-1015 ¶¶117–34, 136–42, 156–62, 169, 176–78; *supra* Section VIII.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).

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 170, 176–78; *infra* Section VIII.R.2.

P. Claim 12

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

PIF in view of West-Ward and Parker discloses the pharmaceutical product that teaches limitations of [7pre]-[7e]. Ex-1015 ¶¶117–34, 156–62, 171; *supra* Section VIII.K.

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

For the reasons described in Element [5a], this element would have been obvious. Ex-1015 ¶¶149–51, 172; *supra* Sections IV.C, VIII.I.2.

Q. Claim 13

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

PIF in view of West-Ward and Parker discloses the pharmaceutical product that teaches limitations of [12pre]-[12a]. Ex-1015 ¶¶117–34, 149–51, 156–62, 171–73; *supra* Section VIII.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).

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 174, 176–78; *infra* Section VIII.R.2.

R. Claim 14

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–34, 143, 175; *supra* Section VIII.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).

As described in Elements [2a] and [4a], Parker teaches that phenobarbital sodium can degrade into harmful impurities like PEAU, 2EPMM, and PBG. Ex-1015 ¶¶136–42, 146–47, 176; *supra* Sections VIII.F.2, VIII.H.2. A POSA would aim to control impurities by reducing water and reactive substances, using lyophilization to minimize hydrolysis and impurities. Ex-1015 ¶¶59–61, 71–76, 136–42, 146–47, 176; *supra* Sections IV.A, IV.C, VIII.F.2, VIII.H.2. PIF demonstrates Nobelbar’s stability under standard long-term storage conditions, providing a framework for monitoring degradants like PEAU, 2EPMM, and PBG. Ex-1015 ¶¶140–41, 146–47, 176–77; *supra* Sections VIII.F.2, VIII.H.2. Specifically, a POSA would have used standard testing conditions, including storing the composition at room temperature for six months, reconstituting in 10 mL of water, and evaluating impurities like PEAU, 2EPMM, and PBG. Ex-1015 ¶¶77–83, 140–41, 146–47, 176–77; *supra* Section IV.D.

Based on Nobelbar’s documented stability, a POSA would expect to minimize PEAU, 2EPMM, and/or PBG to very low levels and certainly no more than 0.05% in a lyophilized phenobarbital sodium composition reconstituted for injection with 10 mL of water after being stored at room temperature for 6 months. Ex-1015 ¶¶136–42, 146–47, 176–78; *supra* Sections VIII.F.2, VIII.H.2.

S. Claim 15

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [14pre]-[14a]. Ex-1015 ¶¶117–34, 136–42, 175–79; *supra* Section VIII.R.

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

For the reasons described in Element [5a], this element would have been obvious. Ex-1015 ¶¶149–51, 180; *supra* Sections IV.C, VIII.I.2.

T. Claim 16

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

PIF in view of West-Ward discloses and renders obvious the limitations of [1pre]-[1d]. Ex-1015 ¶¶117–34, 181; *supra* Section VIII.E.

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

For the reasons described in Elements [1a] and [1b], this element would have been obvious. Ex-1015 ¶¶120–26, 182; *supra* Sections VIII.E.2, VIII.E.3. A POSA would have known that Parker discloses phenobarbital sodium formulations in amounts ranging from 15-200 mg/mL and would have recognized that using a 100 mg dose in a single-use vial is a routine modification within the skill in the art. Ex-1015 ¶¶124, 182-83; *see also Galderma Labs.*, 737 F.3d at 736–39. A POSA would have further known that West-Ward discloses doses of 65 mg/mL and 135

mg/mL and would have been motivated to develop formulations in additional dosage increments, and would have naturally selected 100 mg, the midpoint between the two doses disclosed in West-Ward. Ex-1015 ¶¶124, 183–84. A POSA would have further understood that a vial containing 100 mg of phenobarbital sodium corresponds to a single-use dose for an infant weighing approximately 5 kg (11 pounds), falling between the well-accepted dosages disclosed by Parker and West-Ward, giving the POSA both motivation and a reasonable expectation of success for this element. Ex-1015 ¶¶120–26, 182–84.

U. Claim 17

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [7pre]-[7e]. Ex-1015 ¶¶117–34, 156–62, 185; *supra* Section VIII.K.

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

This element would have been obvious for the reasons set forth with respect to Element [16a]. Ex-1015 ¶¶120–26, 182–84, 186; *supra* Section VIII.T.2.

V. Claim 18

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. Ex-1015 ¶¶117–34, 136–42, 156–64, 176–78, 187; *supra* Section VIII.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).**

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 176–78, 188; *supra* Section VIII.R.2.

W. Claim 19

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. Ex-1015 ¶¶117–34, 136–42, 156–64, 176–78, 189; *supra* Section VIII.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).**

This element would have been obvious for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶136–42, 176–78, 190; *supra* Section VIII.R.2.

X. Claim 20

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

PIF in view of West-Ward and Parker discloses and renders obvious the limitations of [8pre]-[8a]. Ex-1015 ¶¶117–34, 136–42, 156–64, 176–78, 191; *supra* Section VIII.L.

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

For the reasons described in Element [5a], this element would have been obvious. Ex-1015 ¶¶149–51, 192; *supra* Sections IV.C. VIII.I.2.

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

The full scope of the challenged claims is not supported in the Original Applications and, therefore, the challenged claims are not entitled to a priority date before June 30, 2022. The '608 Publication—published more than one year before the June 30, 2022 priority—qualifies as AIA §102(a) prior art and anticipates the challenged claims. Ex-1015 ¶¶193-283.

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

Patent Owner cannot meet its burden to claim priority to the Original Applications.⁵ See *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–81 (Fed. Cir. 2015) (noting that the patent owner has a burden of production to establish an earlier priority and must satisfy the requirements of § 112); see also *Sanofi-Aventis Deutschland GMBH v. Mylan Pharms. Inc.*, Nos. 2020-2066, 2020-2068, 2020-2069, 2021 U.S. App. LEXIS 38482, at *7–9 (Fed. Cir. Dec. 29, 2021); *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362–65 (Fed. Cir. 2018).

To claim priority to an earlier-filed parent application, “the invention claimed must have been disclosed in the parent application in the manner provided by 35 U.S.C. § 112, ¶1.” *Daiichi Sankyo*, IPR-2015-00291, Paper 75 at 4 (citing 35 U.S.C. § 120; *In re Lukach*, 442 F.2d 967, 968-69 (CCPA 1971); *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1344–55 (Fed. Cir. 2010) (en banc)). The

⁵ The Board is authorized to determine the priority date of a patent. See, e.g., *Daiichi Sankyo Co., Ltd v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75 (P.T.A.B. Jun. 14, 2016) at 6 (holding patent was not entitled to the priority date of the parent application).

patent owner bears the burden of demonstrating compliance with § 112.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1303-06 (Fed. Cir. 2008).

For a claim to be entitled to an earlier priority date based off an original parent or grandparent application, the earlier original application must provide a written description of the **full scope** of the claim. *See, e.g., Anascape, Ltd. v. Nintendo of Am., Inc.*, 601 F.3d 1333, 1338–40 (Fed. Cir. 2010) (holding that a CIP application could not claim priority to parent because the original specification limited the invention to a single input member, and the CIP broadened the scope to include multiple input members, which was not supported by the original description).

A specification that provides written description of only a portion of the covered embodiments is insufficient. *See PowerOasis*, 522 F.3d at 1305–10 (holding that the parent application disclosure did not support the broadened asserted claims of the CIP application and therefore the asserted claims were only entitled to the CIP filing date); *see also Hamilton Beach Brands, Inc. v. Sunbeam Prods., Inc.*, No. 3:11-CV-345, 2012 U.S. Dist. LEXIS 97923, at *25–35 (E.D. Va. July 13, 2012).

The Original Applications here do not disclose the **full scope** of the challenged claims because they never taught compositions that contain organic solvents, nor did they teach compositions that include crystalline phenobarbital

sodium. Because each of the challenged claims encompasses such compositions, Patent Owner is not entitled to the priority date of the Original Applications and instead can only claim priority to the filing date of the '914 CIP application: June 30, 2022.⁶

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

To establish written description, the patent owner must show that the patent specification “clearly allow[s] persons of ordinary skill in the art to recognize that [the inventors] invented what is claimed,” *i.e.*, it must “reasonably convey[] to those skilled in the art that the inventor[s] had possession of the claimed subject matter as of the filing date.” *Ariad*, 598 F.3d at 1351 (Fed. Cir. 2010). “Entitlement to a filing date extends only to subject matter that is disclosed; not to that which is obvious. . . . Therefore the parent application must actually or inherently disclose the elements of the later-filed claims.” *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 870 (Fed. Cir. 2010) (internal citations omitted.)

The Federal Circuit has made clear that “claims may be no broader than the supporting disclosure, and therefore that a narrow disclosure will limit claim

⁶ Consequently, the '608 Publication—published on March 25, 2021 as the publication of the '881 application, and more than one year before the priority date of the '076 Patent—qualifies as § 102(a) prior art.

breadth.” *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998). “[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.” *Ariad*, 598 F.3d at 1353–54 (internal quotations omitted). Thus, to claim the benefit of an earlier priority date based on a preceding application, the earlier disclosure must “reasonably convey to one of ordinary skill in the art that the inventors possessed the later-claimed subject matter *when they filed the earlier application*.” *In re Curtis*, 354 F.3d 1347, 1351 (Fed. Cir. 2004) (emphasis added).

2. The Original Applications Lack Written Description for Compositions Containing an Organic Solvent

Patent Owner did not merely fail to disclose organic solvents in the Original Applications; it *expressly excluded* them from the lyophilized amorphous phenobarbital sodium compositions disclosed therein. Ex-1003 at 19 (¶[0078]); Ex-1004 at 210 (¶[00101]), 1213, 1215; *see also* Ex-1015 ¶¶204–09. None of the Disclosures, Examples, Tables, or Figures disclose any lyophilized compositions containing an organic solvent. *See generally* Ex-1003; Ex-1004.

“Organic solvent” with respect to the allegedly disclosed invention appears in the Original Applications two times. First, with respect to the prior art, Patent Owner said, “[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); Ex-1015 ¶205.

Second, the Original Applications said, “[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); Ex-1015 ¶205. Patent Owner thus *distinguished* its disclosed compositions from other phenobarbital sodium formulations on the basis that they excluded “organic solvents” and noted that organic solvents are “not desirable” and “not suitable for administration to newborns.” Ex-1003 at 7 (¶[0007]); Ex-1004 at 195 (¶[0008]) (same); Ex-1015 ¶205.

Consistent with its disclosure, the claims of the ’598 Patent, which issued from the Original Applications, expressly exclude organic solvents. Ex-1015 ¶206; Ex-1006 at cls. 1–15. The Original Applications’ disclosure of lyophilized phenobarbital sodium compositions excluding organic solvents does not reasonably convey that the inventors, as of the 2019 and 2020 filing dates of the Original Applications, possessed the broad pharmaceutical products encompassed by the

challenged claims, including those that *include* organic solvents. *Ariad*, 598 F.3d at 1350–52; Ex-1015 ¶¶204–09.

There is no doubt that Patent Owner did not believe its alleged invention included lyophilized phenobarbital sodium compositions containing organic solvents when it filed the Original Applications. Patent Owner’s new matter, first appearing in the ’914 CIP Application, contained Tables 31 and 32 which include data from experiments conducted by Patent Owner using organic solvents as early as 2019. Ex-1001 at Tables 31–32; *see also* Ex-1007 at 63–65 (¶¶[00172]–[00175]); Ex-1050. Thus, despite the availability of this data prior to the filing of the Original Applications, Patent Owner deliberately omitted it and included *only* data from formulations that were free of organic solvents. Only after Patent Owner learned of Petitioner’s interest in phenobarbital sodium products did Patent Owner resurrect its disregarded data to try to obtain broader patent claims. This underscores that Patent Owner, itself, believed its invention was limited to formulations devoid of organic solvents and prepared the Original Applications accordingly.

3. The Original Applications Lack Written Description for Compositions Having Crystalline Phenobarbital Sodium

The Original Applications also lack written description for the full scope of claims 1–4, 6–11, 13–14, and 16–19 because the Original Applications only disclosed amorphous formulations. Ex-1015 ¶¶210–16. Not one of the Disclosures, Examples, Tables, or Figures disclosed any compositions containing lyophilized

crystalline phenobarbital sodium. *See generally* Ex-1003; Ex-1004; *see also* Ex-1015 ¶¶210–16. Instead, the Original Applications repeatedly affirmed that their alleged invention was limited to *amorphous* compositions. Ex-1003 at 8 (¶[0009]), 9 (¶[0014]), 10 (¶[0022]), 11 (¶¶[0023]-[0024]), 16 (¶[0070]), 19 (¶[0078]), 34; Ex-1004 at 196 (¶¶[0010]-[0011]), 197 (¶[0017]), 199 (¶[0025]), 205 (¶[0073]), 207 (¶[0081]), 209 (¶[0096]), 210 (¶[00101]), 233; *see also* Ex-1015 ¶¶210–16.

Below are illustrative excerpts:

- “A composition of, method for producing, and use of an *amorphous* lyophilized Phenobarbital Sodium having high purity are presented.” Ex-1003 at 34; Ex-1004 at 233 (emphasis added).
- “The contemplated composition is an *amorphous* lyophilized Phenobarbital Sodium with high stability and purity.” Ex-1003 at 8 (¶[0009]); Ex-1004 at 196 (¶[0010]) (emphasis added).
- “The lyophilized *amorphous* formulation that was produced resulted in surprising, unexpected and desirable results.” Ex-1004 at 196 (¶[0011]) (emphasis added).
- “According to contemplated embodiments as disclosed herein, the *amorphous* lyophilized Phenobarbital Sodium composition is stable up to at least 6 months...” Ex-1003 at 9 (¶[0014]); Ex-1004 at 197 (¶[0017]) (emphasis added).

Ex-1015 ¶210. All claims that issued from the Original Applications were expressly limited to “amorphous” compositions. Ex-1006 at cls. 1–15; Ex-1015 ¶211.

The term “crystalline” appears in the specifications of the Original Applications four times. First, to describe prior art *liquid* formulations, Patent Owner stated “Phenobarbital Sodium is typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent.” Ex-1003 at 6 (¶[0004]); Ex-1004 at 194 (¶[0005]); Ex-1015 ¶212. This does not refer to the disclosed lyophilized phenobarbital sodium compositions.

Second, to contrast conventional wisdom, Patent Owner said, “[t]hese results [regarding the alleged superior stability of amorphous compositions] 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]); Ex-1015 ¶212. This contrast between the disclosed amorphous lyophilized phenobarbital sodium compositions and the conventional crystalline forms highlights Patent Owner’s focus on amorphous compositions, to the exclusion of crystalline compositions. Ex-1015 ¶212.

Third, when describing USP grade phenobarbital in the prior art, Patent Owner said, “[s]tructurally, the analyzed USP grade P API (Siegfried, USA) is

polymorphous—containing both crystalline and non-crystalline material.” Ex-1003 at 17 (¶[0071]); Ex-1004 at 205–06 (¶[0074]); Ex-1015 ¶212. This refers to the active pharmaceutical ingredient (“API”) alone and does not refer to the disclosed lyophilized phenobarbital sodium compositions.

Fourth, Patent Owner teaches that the “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); Ex-1015 ¶212.

There is not a single instance where Patent Owner used the term “crystalline” to refer to any alleged inventive composition of the Original Applications. Rather, Patent Owner repeatedly described the alleged inventive composition as “non-crystalline.” Without fail, Patent Owner used the term to distinguish crystalline forms from the *amorphous* forms. Ex-1015 ¶212.

Patent Owner may attempt to argue that the Original Applications’ disclosure 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%,” discloses crystalline forms by negative implication. Ex-1015 ¶213; Ex-1004 at 196 (¶[0012]). But that disclosure does not show that Patent Owner possessed crystalline forms. *See Tronzo v. Biomet*, 156 F.3d 1154, 1158 (Fed. Cir. 1998) (“A disclosure in a parent application that merely renders the later-

claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations.”). Nor does it show that Patent Owner was claiming crystalline forms as part of its allegedly inventive compositions, which were repeatedly *distinguished* in the Original Applications. *See* Ex-1003 at 19 (¶[0078]), 112 (Fig. 5D); Ex-1004 at 210 (¶[00101]), 272 (Fig. 5D).

Patent Owner reaffirmed during prosecution that its allegedly inventive compositions were limited to amorphous phenobarbital sodium—and not crystalline forms—by relying on the advantageous properties of non-crystalline formulations:

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); Ex-1015 ¶214. The Patent Office agreed, affirming its understanding that the “*crystalline form* [of

phenobarbital sodium] is *not the claimed subject matter* [of the '881 application].”

Ex-1004 at 658 (emphasis added); Ex-1015 ¶214.

In short, there is no written description in the Original Applications for any claims that are not limited to amorphous phenobarbital sodium. Ex-1015 ¶¶210–17.

4. Patent Owner Cannot Claim Priority for Claims that Include Compositions Not Disclosed in the Original Applications

Patent Owner will, no doubt, argue that it is entitled to claim priority to the Original Applications for the challenged claims because the Original Applications described formulations that fall within the scope of the challenged claims. While it is true that the Original Applications disclosed *some* formulations that are within the scope of the challenged claims, it is abundantly clear that the Original Applications failed to describe the *full scope* of the challenged claims because they excluded compositions containing organic solvents and did not disclose any crystalline compositions. Moreover, not only did Patent Owner fail to disclose any such compositions in the Original Applications, Patent Owner also frequently and expressly highlighted the importance of excluding organic solvents and using amorphous formulations to its purported invention.

The Federal Circuit has repeatedly recognized that removing a limitation described in the disclosure as important to the invention, as Patent Owner did here with respect to the exclusion of organic solvents and requirement for amorphous

formulations, results in (broader) claims that do not meet the written description requirement of § 112. For example, in *Gentry Gallery v. Berkline*, claims to a sectional sofa comprising, *inter alia*, a console and a control means were held invalid for failing to satisfy the written description requirement where the claims were broadened by removing the location of the control means. 134 F. 3d 1473. Similarly, in *Tronzo v. Biomet*, the Federal Circuit concluded that claims to a generic cup shape were not entitled to the filing date of a parent application that disclosed only a “conical cup” in view of the disclosure of the parent application stating the advantages and importance of the conical shape. 156 F.3d at 1158–59; *see also PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1248 (Fed. Cir. 2002) (claim for a method of inhibiting sprout growth on tubers by treating them with spaced, sequential application of two chemicals was held invalid for lack of adequate written description where the specification indicated that invention was a method of applying a “composition” containing the two chemicals); *In re Wilder*, 736 F.2d 1516 (Fed. Cir. 1984) (reissue claim omitting “in synchronism” limitation with respect to scanning means and indexing means was not supported by the original patent’s disclosure in such a way as to indicate possession of that generic invention); MPEP § 2163 (“A claim that omits an element that applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement.”).

Furthermore, the Federal Circuit has established that criticizing claim elements and emphasizing the need for an alternative approach in an earlier application, as Patent Owner did here with respect to the presence of organic solvents, can break the priority chain due to lack of written description in the claimed priority application. In *Arthrex, Inc. v. Smith & Nephew, Inc.*, the Federal Circuit held that a patent's claims were anticipated by a prior related application because the earlier application's specification criticized the use of a "flexible" eyelet and exclusively described alternatives, such as a more rigid eyelet, to overcome its disadvantages, but the later claims were broad enough to encompass the use of rigid *or* flexible eyelets. 35 F.4th 1328, 1343–44 (Fed. Cir. 2022). Aside from this critique, the earlier application was silent on "flexible" eyelets. *Id.* The Court found that the criticism provided substantial evidence that the application lacked written description for the broader claim of "generic" eyelets in the challenged patent, breaking the priority chain and rendering the earlier application anticipatory. *Id.*

Here, the fact that the Original Applications only disclosed compositions that excluded organic solvents, and that they expressly recognized that the inclusion of organic solvents is "not desirable," means that they do not show possession by Patent Owner at the time of the Original Applications of the broader set of compositions later claimed in the challenged claims. *See also, Bamberg v.*

Dalvey, 815 F.3d 793 (Fed. Cir. 2016) (affirming PTAB decision of no written description support for claims including white layers that melt below or above 220°C where disclosure “does not possess a white layer that melts below 220°C because it specifically distinguished white layers that melt below 220°C as producing an ‘undesired’ result”) (citation omitted).

Similarly, with respect to compositions that are crystalline, while Patent Owner did not overtly criticize crystalline formulations in the Original Applications as it did with organic solvents, Patent Owner clearly described its invention as being limited to amorphous formulations. In *Research Corp. Techs. v. Microsoft Corp.*, the Federal Circuit found that an earlier priority patent application disclosing only a “blue noise mask” was insufficient to support later-filed claims encompassing “blue noise dot profiles” where all dot profiles did not have to have blue noise characteristics. 627 F.3d 859, 871 (Fed. Cir. 2010). In concluding that the claims were not supported by the original applications, the Federal Circuit noted that “the specifications repeatedly refer to a blue noise mask as ‘the present invention’” and that such “references to ‘the present invention’ strongly suggest that the claimed invention is limited to a blue noise mask.” *Id.* at 871–72.

Similarly, in *ICU Med., Inc. v. Alaris Med. Sys.*, the Federal Circuit affirmed summary judgment of invalidity because a specification describing only medical valve embodiments with spikes did not support claims that were silent as to a spike

limitation, making them broad enough to cover both spike and spikeless designs. 558 F.3d 1368, 1378 (Fed. Cir. 2009). The Federal Circuit concluded that “[b]ased on this disclosure, a person of ordinary skill in the art would not understand the inventor . . . to have invented a spikeless medical valve.” *Id.* Here, the focus of the Original Applications’ disclosure on amorphous formulations demonstrates that Patent Owner understood and communicated to a POSA that its invention was limited to amorphous compositions.

B. Because the Priority Date of the Challenged Claims is June, 30, 2022, they are anticipated by the ’608 Publication

The challenged claims lack support in the Original Applications and are not entitled to a priority date before June 30, 2022. The ’608 Publication—published more than one year before the June 30, 2022 priority—qualifies as § 102(a) prior art and, as explained in detail below, anticipates the challenged claims. Ex-1015 ¶¶193–94, 218–28, 229–83.

1. Claim 1

a. [1pre]

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 *passim*; Ex-1015 ¶¶229–30.

b. [1a]

The '608 Publication discloses aliquoting phenobarbital sodium into “single use dose vials for lyophilization.” Ex-1005 at [0079]; *see also id.* at cl. 15; Ex-1015 ¶231.

c. [1b]

The '608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg. Ex-1005 at [0025]; *see also id.* at *passim*; Ex-1015 ¶232.

d. [1c]

The '608 Publication discloses compositions of, methods of producing, and use of a sterile and lyophilized amorphous phenobarbital sodium formulation with high stability and purity. Ex-1005 at [0010], [0013]; *see also id.* at *passim*; Ex-1015 ¶233.

e. [1d]

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]; Ex-1015 ¶234.

2. Claim 2

a. [2pre]

The '608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–36; *supra* Section IX.B.1.

b. [2a]

The '608 Publication discloses this element. Specifically, it discloses storage stable lyophilized compositions of phenobarbital sodium salt 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; Ex-1015 ¶237. The '608 Publication further discloses that, once the lyophilized phenobarbital sodium has been reconstituted after storage for six months at “accelerated stability conditions (ACC),” the reconstituted solution forms “no more than 0.1% phenylethylacetylurea (PEAU).” Ex-1005 at [0016], [0088]; *see also id. at passim*; Ex-1015 ¶237. The '608 Publication discloses that the tested accelerated stability conditions are 40°C and 75% relative humidity (“RH”). Ex-1005 at [0013]; *see also id. at passim*; Ex-1015 ¶237.

3. Claim 3

a. [3pre]

The '608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–35, 238; *supra* Section IX.B.1.

b. [3a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶239, 270; *infra* Section IX.B.14.B.

4. Claim 4

a. [4pre]

The '608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–35, 240; *supra* Section IX.B.1.

b. [4a]

The '608 Publication discloses this element. Specifically, it discloses storage-stable lyophilized phenobarbital sodium compositions with high purity that do not form any significant amount of toxic degradation products, such as 2EPMM or PBG, upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1015 ¶¶237, 241; *supra* Section IX.B.2.

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 . . . [at] accelerated stability conditions” of 40°C and 75% RH. Ex-1005 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; Ex-1015 ¶¶237, 241.

5. Claim 5

a. [5pre]

The ’608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–35, 242; *supra* Section IX.B.1.

b. [5a]

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 *passim*; Ex-1015 ¶243.

6. Claim 6

a. [6pre]

The ’608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–35, 244; *supra* Section IX.B.1.

b. [6a]

The ’608 Publication discloses this element. Specifically, it discloses storage-stable lyophilized phenobarbital sodium compositions with high purity that do not form any significant amount of toxic degradation products, such as PEAU

upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1015

¶¶237, 245; *supra* Section IX.B.2.

The '608 Publication further discloses that the lyophilized phenobarbital sodium upon reconstitution after storage “for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC)” forms “no more than 0.1% phenylethylacetylurea (PEAU).” Ex-1005 at [0016], [0088]; Ex-1015 ¶¶237, 245; *supra* Section IX.B.2. The '608 Publication discloses that “at least 6 months under accelerated stability conditions [] is equivalent to 24 months at [room temperature].” Ex-1005 at [0017], [0071], [0091], [0101]; *see also id.* at cl. 11; Ex-1015 ¶245. This element is expressly disclosed.

The '608 Publication also inherently disclosed this element because it identifies specific batches (e.g., Batch# NPH2020, Batch# NPH1980, Batch# NPH1912) that were shown to satisfy this element upon measuring their stabilities after 24 months. Ex-1015 ¶¶246–48.

7. Claim 7

a. [7pre]

The '608 Publication discloses this element. Ex-1015 ¶¶229–30, 250–51; *supra* Section IX.B.1.1.

b. [7a]

The '608 Publication discloses this element. Ex-1015 ¶¶231, 252; *supra* Section IX.B.1.2.

c. [7b]

The '608 Publication discloses this element. Ex-1015 ¶¶232, 253; *supra* Section IX.B.1.3.

d. [7c]

The '608 Publication discloses this element. Ex-1015 ¶¶233, 254; *supra* Section IX.B.1.4.

e. [7d]

The '608 Publication discloses this element. Ex-1015 ¶¶234, 255; *supra* Section IX.B.A.5.

f. [7e]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶256, 270; *infra* Section IX.B.14.b.

8. Claim 8

a. [8pre]

The '608 Publication discloses the pharmaceutical product of claim 7. Ex-1015 ¶¶229–35, 250–57, 270; *supra* Section IX.G.

b. [8a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶258, 270; *infra* Section IX.B.14.b.

9. Claim 9

a. [9pre]

The '608 Publication discloses the pharmaceutical product of claim 7. Ex-1015 ¶¶229–35, 250–56, 259, 270; *supra* Section IX.G.

b. [9a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶260, 270; *infra* Section IX.B.14.b.

10. Claim 10

a. [10pre]

The '608 Publication discloses the pharmaceutical product of claim 7. Ex-1015 ¶¶229–35, 250–56, 261, 270; *supra* Section IX.B.7.

b. [10a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶262, 270; *infra* Section IX.B.14.b.

11. Claim 11

a. [11pre]

The '608 Publication discloses the pharmaceutical product of claim 10. Ex-1015 ¶¶229–35, 250–56, 261, 263, 270; *supra* Section IX.B.10.

b. [11a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶264, 270; *infra* Section IX.B.14.b.

12. Claim 12

a. [12pre]

The '608 Publication discloses the pharmaceutical product of claim 7. Ex-1015 ¶¶229–35, 250–56, 265, 270; *supra* Section IX.B.7.

b. [12a]

The '608 Publication discloses this element. Ex-1015 ¶¶243, 266; *supra* Section IX.B.5.b.

13. Claim 13

a. [13pre]

The '608 Publication discloses the pharmaceutical product of claim 12. Ex-1015 ¶¶229–35, 243, 250–56, 265–67, 270; *supra* Section IX.B.12.

b. [13a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶268, 270; *infra* Section IX.B.14.b.

14. Claim 14

a. [14pre]

The '608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229–35, 269; *supra* Section IX.B.1.

b. [14a]

The '608 Publication discloses this element. Specifically, it discloses storage-stable lyophilized phenobarbital sodium compositions with high purity that

do not form any significant (not measurable or not detectable) amount of toxic degradation products, such as PEAU, 2EPMM, or PBG upon reconstitution in 10 mL of Water for Injection or 5% Dextrose. Ex-1005 at Abstract, [0002], [0073], [0101], [0119]; *see id.* at passim; Ex-1015 ¶270. The '608 Publication further discloses that the lyophilized phenobarbital sodium upon reconstitution after storage “for up to 6 months at [room temperature] and accelerated stability conditions” 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).” Ex-1005 at [0016]; *see also id.* at passim; Ex-1015 ¶270. The '608 Publication further discloses that the lyophilized phenobarbital sodium upon reconstituted after storage “for up to 6 months at room temperature (RT)” forms “no more than 0.05% PEAU.” Ex-1005 at [0016]; *see also id.* at passim; Ex-1015 ¶270.

15. Claim 15

a. [15pre]

The '608 Publication discloses the pharmaceutical product of claim 14. Ex-1015 ¶¶229–35, 269–71; *supra* Section IX.B.14.

b. [15a]

The '608 Publication discloses this element. Ex-1015 ¶¶243, 272; *supra* Section IX.B.5.b.

16. Claim 16

a. [16pre]

The '608 Publication discloses the pharmaceutical product of claim 1. Ex-1015 ¶¶229-35, 273; *supra* Section IX.B.1.

b. [16a]

The '608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 100 mg in single use vials. Ex-1005 at [0025], [0079], [0099]; *see id.* at [0075], [0093], [0105], [0106], [0119], Tables 6, 17, cls. 13, 15, 19; Ex-1015 ¶274.

17. Claim 17

a. [17pre]

The '608 Publication discloses the pharmaceutical product of claim 7. Ex-1015 ¶¶229–35, 250–56, 270, 275; *supra* Section IX.B.7.

b. [17a]

The '608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 100 mg in single use dose vials. Ex-1015 ¶¶274, 276; *supra* Section IX.B.16.b.

18. Claim 18

a. [18pre]

The '608 Publication discloses the pharmaceutical product of claim 8. Ex-1015 ¶¶229–35, 250–58, 270, 277; *supra* Section IX.B.8.

b. [18a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶270, 278; *supra* Section IX.B.14.b.

19. Claim 19

a. [19pre]

The '608 Publication discloses the pharmaceutical product of claim 8. Ex-1015 ¶¶229–35, 250–58, 270, 279; *supra* Section IX.B.8.

b. [19a]

The '608 Publication discloses this element for the reasons set forth with respect to Element [14a]. Ex-1015 ¶¶270, 280; *supra* Section IX.B.14.b.

20. Claim 20

a. [20pre]

The '608 Publication discloses the pharmaceutical product of claim 8. Ex-1015 ¶¶229–35, 250–58, 281; *supra* Section IX.B.8.

b. [20a]

The '608 Publication discloses this element. Ex-1015 ¶¶270, 282; *supra* Section IX.B.5.b.

As a result, the challenged claims are anticipated by the '608 Publication. Ex-1015 ¶¶229–83.

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

As described above in connection with Ground 2, the '608 Publication is prior art to the challenged claims. *Supra* Section IX.A. To the extent Patent Owner argues that any element of the challenged claims is not expressly disclosed in the '608 Publication, any such element(s) would have been obvious based on the '608 Publication alone in light of the ordinary knowledge of a person or ordinary skill in the art. Ex-1015 ¶¶284–373.

A POSA would have been motivated to develop the compositions of the '608 Publication because they reportedly were “desirable” and allegedly had superior stability compared to prior phenobarbital sodium compositions. Ex-1005 at [0011]; Ex-1015 ¶289. More specifically, the teachings of the '608 Publication would have motivated a POSA to develop a storage-stable pharmaceutical product comprising highly pure, sterile, lyophilized amorphous phenobarbital sodium compositions with low levels of impurities, containing more than 98% phenobarbital sodium, with a shelf-life of at least two years. Ex-1015 ¶¶229–35, 242–43, 250–58, 265–66, 269–72, 281–82, 288–94, 296–312, 323–25, 334–43, 354–59, 350–51, 360–61, 371–72; *supra* Sections IX.B.1, IX.B.5, IX.B.7, IX.B.12, IX.B.15, IX.B.20.

The '608 Publication would have further motivated a POSA to aliquot phenobarbital sodium into single use dose vials in a 65 mg dose, a 100 mg dose, a

130 mg dose, or a 200 mg dose. Ex-1015 ¶¶229–35, 250–56, 270, 273–76, 295, 300–12, 334–41, 354–59, 362–66; *supra* Sections IX.B.1, IX.B.7, IX.B.16, IX.B.17.

A POSA would have known from the '608 Publication of phenobarbital sodium's risk of hydrolysis and its potential to produce degradants. Ex-1005 at [0006], [0011], [0017], [0023], [0073]; Ex-1015 ¶290. From the '608 Publication, the POSA would have known that lyophilization enhances stability of amorphous phenobarbital sodium and reduces impurities, including PEAU, 2EPMM, and PBG. Ex-1015 ¶¶229–41, 244–70, 277–80, 288–92, 296–98, 300–22, 326–49, 350–59, 367–70; *supra* Sections IX.B.2–4, IX.B.6–11, IX.B.13–14, IX.B.18–19. Thus, a POSA would have been motivated while developing a lyophilized phenobarbital sodium product to identify, screen, and minimize these toxic degradants (including down to as low as no more than 0.05%). Ex-1015 ¶¶290, 292, 296–99; *see also* *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301–02 (Fed. Cir. 2007); *Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1334–35 (Fed. Cir. 2015). Recognizing that lyophilized phenobarbital sodium is typically administered intravenously or intramuscularly, a POSA would have also been especially driven to sterilize the composition and reduce impurities to the lowest possible level. Ex-1015 ¶¶234, 255, 294, 310–11, 340; *supra* Sections IX.B.1.d, IX.A.7.d.

The '608 Publication teaches that lyophilized phenobarbital sodium is storage-stable for up to six months at room temperature and under accelerated stability conditions (at 40°C, 75% RH), which is a proxy for 24 months at room temperature. Ex-1015 ¶¶229–41, 244–70, 277–80, 291–92, 300–22, 326–49, 350–59, 367–70; *supra* Sections IX.B.2–4, IX.B.6–11, IX.B.13–14, IX.B.18–19. A POSA would have been motivated to ensure the compositions had a shelf life of at least 2 years and would have, as a matter of routine, monitored and tested the stability of the disclosed batches for at least two years. Ex-1015 ¶292. Accordingly, a POSA would have been motivated, with a reasonable expectation of success, based on, *inter alia*, the known benefits of lyophilization and reported accelerated stability testing, to further improve the formulation's stability, to create a lyophilized phenobarbital sodium composition that is stable for up to at least 24 months at room temperature and essentially free of impurities, such as PEAU, 2EPMM, and PBG, upon reconstitution with 10 mL of an aqueous solution. Ex-1015 ¶292.

Consequently, a POSA would have been motivated and had a reasonable expectation of success to develop a formulation that meets the requirements of the challenged claims. Ex-1015 ¶373.

XI. THERE ARE NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

No objective indicia exists with respect to the '076 patent to overcome the strong *prima facie* case of obviousness set forth above with respect to Ground 1 or Ground 3. *See* Ex-1015 ¶¶374–81.

To rely on objective indicia, Patent Owner must establish a nexus between the evidence and the merits of the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). Patent Owner cannot establish either the existence of any objective indicia of nonobviousness or a nexus. Should Patent Owner try to argue against the obviousness of any of the challenged claims based on objective indicia of obviousness, Petitioner reserves the right to fully address any such argument.

XII. TRIAL SHOULD BE INSTITUTED (35 U.S.C. §§ 314(a), 325)

Pursuant to Acting Director Coke M. Stewart's March 26, 2025, Memorandum regarding Interim Processes for PTAB Workload Management, Petitioner understands that discretionary denial issues, if any, will be addressed in a separate brief to be filed by Patent Owner. Accordingly, Petitioner does not address such issues in detail here.

Even if Patent Owner were to argue for discretionary denial, there is no basis to do so under 35 U.S.C. §§ 314(a) or 325. The '076 patent is the *only* patent asserted in the district court action, and Petitioner intends to immediately seek to

stay if this challenge is instituted. Moreover, while there is a trial date currently scheduled for February 2026, the Patent Owner filed the district court action in the wrong venue. Petitioner has filed a motion to dismiss or transfer to the District of New Jersey that is particularly strong. Ex-1048.

In addition, the Grounds of this Petition are not cumulative of art or arguments considered during prosecution. Ex-1015, ¶¶384-392. The PIF reference of Ground 1 was not before the Examiner during prosecution. While another reference related to Nobelbar's product was included in a Third-Party Submission in prosecution, it was not addressed or discussed by either the Examiner or the Applicants. *E.g.*, Ex-1015 ¶385 and n.11. Moreover, the Examiner did not identify the '608 Publication (the subject of Grounds 2-3) as prior art. As a result, the Applicants' own invalidating disclosure was not addressed at all.

If Patent Owner contends that discretionary denial is warranted, Petitioner reserves the right to and intends to respond in an opposition brief consistent with the Acting Director's guidance in the March 26, 2025 Memorandum.

XIII. CONCLUSION

For the reasons above, the Board should cancel the challenged claims as unpatentable.

XIV. MANDATORY NOTICES

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

Sun Pharmaceutical Industries, Inc. is the real party-in-interest. Three other Sun entities were also named in the district court action, namely Sun Pharmaceutical Industries, Ltd., Sun Pharma Advanced Research Company Ltd., and Sun Pharmaceutical Medicare Ltd. Based on a stipulation of the parties, each has been dismissed pursuant to Federal Rule of Civil Procedure 41(a)(1)(A)(ii).

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

The '076 Patent is the subject of pending litigation: *Nivagen, Inc. v. Sun Pharmaceuticals Industries, Inc.*, No. 2:24-cv-36-RWS-RSP (E.D. Tex.); however, the Plaintiff in the litigation, “Nivagen, Inc.” has a different name from that listed in the U.S. Patent and Trademark Office’s Patent Assignment Database, “Nivagen Pharmaceuticals, Inc.,” as an assignee for the '076 Patent. Ex-1049.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	Back-Up Counsel
J. Derek Vandenberg, Reg. No. 32,179 Carlson Caspers Vandenberg & Lindquist 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 dvandenberg@carlsoncaspers.com (612) 436-9618	Alexandra J. Olson, Reg. No. 75,389 Carlson Caspers Vandenberg & Lindquist 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 aolson@carlsoncaspers.com (612) 436-9645 Samuel T. Lockner, <i>Pro Hac Vice</i> to be submitted

	Carlson Caspers Vandenburg & Lindquist 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 slockner@carlsoncaspers.com (612) 436-9654 Peter M. Kohlhepp, <i>Pro Hac Vice</i> to be submitted Carlson Caspers Vandenburg & Lindquist 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 pkohlhepp@carlsoncaspers.com (612) 436-9659
--	---

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney for Petitioner has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Service of any documents via hand-delivery or postal mailing may be made at the mailing address of lead and backup counsel designated above. Petitioner consents to electronic service at the e-mail addresses of lead and backup counsel designated above.

XV. PAYMENT OF FEES

Pursuant to 37 C.F.R. §§ 42.103 and 42.15(a), the required fee is being submitted herewith.

XVI. WORD COUNT

Under 37 C.F.R. § 42.24(d), Petitioner certifies that this Petition for *Inter Partes* Review has a word count of 13,724, excluding the portions exempted by 37 C.F.R. § 42.24(a), as calculated by the built-in word-count function in the Microsoft Word software used to prepare this document, and a manual count of the number of words appearing in the figures.

XVII. CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on April 22, 2025, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,878,076, Power of Attorney, Exhibit List, and all supporting exhibits were served via FedEx on Patent Owner by serving the correspondence address of record indicated in the Patent Office's Patent Center for U.S. Patent No. 11,878,076:

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92514
United States of America

A courtesy copy was also sent to the above-referenced firm by email to the attorneys at the following email addresses:

- tsmith@umbergzipser.com
- patents@umbergzipser.com
- rdean@umbergzipser.com
- mfessenmaier@umbergzipser.com
- mtsang@umbergzipser.com

- pphukan@umbergzipser.com
- dmcmillan@umbergzipser.com

A courtesy copy of the foregoing was also served via email upon the following counsel of record for the Patent Owner in litigation pending before the United States District Court for the Eastern District of Texas Case No. 2:24-cv-36-RWS-RSP:

Shashank Upadhye
Yixin Tang
Brent Batzer
UPADHYE TANG LLP
109 Symonds Dr. #174
Hinsdale, IL 60522
shashank@ipfdalaw.com
yixin@ipfdalaw.com
brent@ipfdalaw.com

A courtesy copy of the foregoing was also served via FedEx upon Patent Owner Nivagen Pharmaceuticals, Inc. at its corporate address:

Attn: General Counsel/Chief Legal Officer
Nivagen Pharmaceuticals, Inc.
3050 Fite Cir. Suite 100
Sacramento, CA 95827

Date: April 22, 2025

Respectfully submitted,

/J. Derek Vandenburg/

J. Derek Vandenburg

Registration No. 32,179

CARLSON, CASPERS, VANDENBURGH &
LINDQUIST, P.A.

225 South Sixth Street, Suite 4200

Minneapolis, MN 55402

Telephone: (612) 436-9618

Facsimile: (612) 436-9605

Email: dvandenburg@carlsoncaspers.com

Lead Counsel for Petitioner

Appendix A

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 (2EPMMA).
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.