CONFIDENTIAL

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

NIVAGEN, INC., Plaintiff v. SUN PHARMACEUTICALS INDUSTRIES, INC., Defendant.	Case No.: 2:24-cv-36-RWS-RSP **JURY TRIAL DEMANDED**

SUN'S INVALIDITY CONTENTIONS (LOCAL PATENT RULE 3-3)

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I. INTRODUCTION

Pursuant to the Scheduling Order and Local Patent Rule 3-3 before the United States District Court for the Eastern District of Texas ("L. Pat. R." or "Local Patent Rule"), Defendant Sun Pharmaceuticals Industries, Inc. ("Sun") hereby serves its Invalidity Contentions for United States Patent Nos. 11,406,598 ("the '598 Patent") and 11,878,076 ("the '076 Patent") (collectively, the "Patents-in-Suit").

Plaintiff Nivagen, Inc. ("Nivagen" or "Plaintiff") has asserted claims 1-3, 6, 10, 12-15 of the '598 Patent and claims 1-20 of the '076 Patent (collectively, the "Asserted Claims") against Sun in Plaintiff's Disclosure of Asserted Claims and Infringement Contentions dated August 12, 2024. In the event Plaintiff is later allowed to assert additional or different claims or patents, Sun reserves the right to address the invalidity of those claims or/and patents.

The Invalidity Contentions are based, in part, upon the information in Sun's possession as of the date of the Invalidity Contentions, which is at the start of fact discovery and months before the deadline for fact discovery and even further from expert discovery. Sun reserves the right to supplement its defenses set forth herein with additional evidence gained during fact and expert discovery and to assert any additional defense(s) that discovery reveals. Each of the claims of the Patents-in-Suit is invalid. With respect to each claim, and based on its investigation to date, Sun hereby: (a) identifies prior art that renders each claim anticipated or obvious; (b) for each item of prior art governed by 35 U.S.C. § 102(b), specifies the item offered for sale or publicly used or known, the date the offer or use took place or such information became known, and the person or entity who used the item or made and received the offer, or the person or entity which made such information known or to whom such information was made known; (c) explains why the prior art

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renders the claim anticipated or obvious, and for the latter, identifies exemplary combinations[1] of prior art showing obviousness, including the motivation to combine such prior art; (d) submits a chart for each Patents-in-Suit (**Exhibits A1-B9**) identifying where specifically in each alleged item of prior art each element of each of the claim is found. In the contentions and claim charts that follow, the analysis for any dependent claim also incorporates the analysis for any claim from which the dependent claim depends. This includes all prior art and non-prior art defenses.

In connection with its Invalidity Contentions, Sun has produced documents bearing Bates nos. SUNSZBY0000001 - SUNSZBY0039930 pursuant to Local Patent Rule 3-4.

To the extent these contentions or any documents in connection with these contentions contain any information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, or any other applicable privilege or immunity, such disclosure is inadvertent and does not, nor is it intended to, constitute a waiver of any such privilege or immunity.

II. GENERAL CONSIDERATIONS

A. Confidentiality

Pursuant to the Protective Order entered in this Action, these contentions are designated "Confidential."

B. Identification of Asserted Claims

Plaintiff asserts that Sun's Sezaby product infringes the following claims of the Patents-in-Suit:

[1] Sun reserves the right to further assert additional or alternative combinations of prior art references for any of the claims of the Patents-in-Suit and to modify the combinations provided as discovery progresses.

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Patents	Asserted Claims
11,406,598	1-3, 6, 10, 12-15
11,878,076	1-20

As set forth herein, each of the above asserted claims is invalid and therefore not infringed by Sun.

To the extent that Plaintiff attempts to assert additional claims or patents and is allowed to do so, Sun reserves the right to respond and to amend or supplement these Invalidity Contentions accordingly.

C. Claim Construction

The parties have not yet identified any claim terms that require construction by the Court nor proposed constructions for any claim terms in the Asserted Claims. The Court has not construed the Asserted Claims or adopted a definition of a person of ordinary skill in the art ("POSA"). Sun reserves the right to amend these Invalidity Contentions based on any claim constructions issued by this Court regarding the Patents-in-Suit. Sun's Invalidity Contentions should not be construed to advocate for or accede to any particular claim construction. Sun specifically reserves the right to request the Court to construe disputed claim terms of the Patents-in-Suit at the appropriate time in the case schedule. Sun expressly reserves the right to supplement or otherwise amend these Invalidity Contentions in the event the Court issues a claim construction ruling on the Patents-in-Suit.

Similarly, nothing stated herein shall be treated as an admission or suggestion that Sun agrees with Plaintiff regarding either the scope of any of the Asserted Claims or the claim constructions advanced directly or implicitly by Plaintiff. Additionally, nothing in these Invalidity Contentions shall be treated as an admission that any of Sun's accused products meet any limitations of the Asserted Claims.

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D. Prior Art Identification and Citation

To focus the issues, Sun identifies only limited portions of the cited references. It should be recognized that a POSA would generally read a prior art reference as a whole and in the context of other publications, literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior art reference, a POSA would rely on other information including other publications and general scientific or engineering knowledge. Indeed, the cited references below may be combined and modified in many obvious ways to achieve the claimed products. Given the obviousness of the claimed subject matter, there are many references in the prior art with overlapping teachings; and if Plaintiff critiques one reference, Sun could easily and reserves the right to rely on another disclosed reference given the advanced state of the art.

Sun incorporates by reference and relies upon all prior art references cited on the face of the Patents-in-Suit.

Sun reserves the right to rely upon any and all portions of the prior art references identified and upon expert testimony and analysis to provide context and to aid understanding and interpretation of the prior art and how it renders the claims of the Asserted Patents obvious and/or anticipated. Sun also reserves the right to rely upon other prior art references, other publications, and the testimony of experts to establish that the alleged inventions would have been obvious to a POSA, including based on modifying or combining certain cited references. Sun also reserves the right to rely upon any admissions relating to prior art in the Patents-in-Suit, the state of the art, the intrinsic properties of the compounds at issue, or the Patents-in-Suit's prosecution histories, and prosecution histories of related patents/applications.

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E. Ongoing Discovery and Disclosures

Discovery in this case is in its initial stages, and Sun's investigation, including Sun's search for prior art, is ongoing. Some relevant information at least preliminarily may some from foreign discovery that may take time to obtain. Sun therefore reserves the right to further supplement, amend, or alter the positions taken and information disclosed in these Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to consider information or defenses that may become known as a result of these continuing efforts, including foreign discovery.

Moreover, because expert discovery has not started, Sun reserves the right to amend these Invalidity Contentions because of new information disclosed through the parties' experts. Additionally, fact discovery is just beginning, and the substantial completion of document production deadline is months away. Therefore, Sun reserves all rights to further supplement, amend, or alter these Invalidity Contentions if, and when, further information becomes available. These Invalidity Contentions are provided without prejudice to the rights of Sun to introduce at trial any subsequently discovered evidence or expert opinions relating to currently known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently discovered facts. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents, and things may not be included in the following Invalidity Contentions. Sun reserves the right to conduct discovery with reference to, or offer into evidence at the time of trial, all facts, expert opinion testimony, documents, and things notwithstanding the written statements herein. Sun further reserves the right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents, and things that are not currently recalled but might be recalled at some time in the future.

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The information set forth below is provided without in any manner waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other actions, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time.

Sun's invalidity positions in these contentions may be in the alternative and do not constitute any concession or admission by Sun for purposes of invalidity, enforceability, claim construction, and/or infringement. *See, e.g., Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000). For example, Sun's Section 112 arguments may be in the alternative to Sun's obviousness arguments and should not be viewed, in any way, to be concessions about the prior art or knowledge of one of ordinary skill in the art.

F. Reservation of Rights

Sun reserves all rights to modify, amend, or otherwise supplement these Invalidity Contentions at any time and for any reason, including with the addition of prior art references, should further discovery, the Court's claim construction, or other circumstances so require. Specifically, the Invalidity Contentions are based on information and belief of what is presently available to Sun, reflecting the statements of the cited prior art references, and Defendant reserves the right to pursue further discovery regarding prior art, including, but not limited to, third-party discovery related to any pharmaceutical product available at the time of the alleged invention. Sun further reserves the right to supplement and/or amend these contentions if Plaintiff asserts claim constructions different from those relied upon by Sun; if Plaintiff is permitted to assert additional or different infringement allegations at a later date; if Plaintiff asserts an interpretation of prior art different from that used herein, including assertions that any

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limitations of the claims of the Patents-in-Suit are not disclosed in the prior art identified herein; and based upon information, documents, things, or electronically stored information produced in this or any other action or regulatory proceeding involving any of the patents at issue in this litigation (whether by Plaintiff or a third party to this action). Sun further reserves the right to modify, amend, or otherwise supplement these Invalidity Contentions, including the addition of prior art references, in accordance with the Federal Rules of Civil Procedure, the Local Rules of the Court, the Court's Scheduling Order, any agreement of the parties, or any order of the Court. Sun further reserves the right to modify, amend, or otherwise supplement these Invalidity Contentions in response to any contentions by Plaintiff, including, for example, infringement contentions, claim construction positions, responsive validity contentions, and the like.

Nothing in this statement of contentions should be construed as limiting Sun's statutory rights under 35 U.S.C. § 282 to provide notice of "the country, number, date, and name of the patentee of any patent, the title, date, and page numbers of any publication to be relied upon as anticipation of the patent in suit or, except in actions in the United States Court of Federal Claims, as showing the state of the art, and the name and address of any person who may be relied upon as the prior inventor or as having prior knowledge of or as having previously used or offered for sale the invention of the patent in suit" thirty days before trial. 35 U.S.C. § 282(c).

Plaintiff has the burden to establish that the claims of the Patents-in-Suit are entitled to the priority date of any earlier-filed application. *See Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015). To establish an earlier priority date, each earlier application in the chain must fully disclose the claimed invention by meeting all requirements of 35 U.S.C. §112. *In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011). Sun reserves the right to (i) challenge any claim by Plaintiff that either of the Patents-in-Suit's is

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entitled to priority to previous applications, (ii) challenge any alleged date of conception or reduction to practice; and (iii) identify additional prior art thereto.

Sun is not aware of any applicable objective indicia of non-obviousness of the claims of the Patents-in-Suit at this stage of the litigation. Sun has no burden at this stage of the litigation to come forward with evidence rebutting such considerations. It is Plaintiff's obligation and burden to come forward with evidence of objective indicia of non-obviousness, if any, on which it intends to rely. Sun reserves all rights to respond to any objective indicia of non-obviousness that Plaintiff may later assert and reserves all rights to respond to and rely upon further references not cited herein to rebut those objective indicia of non-obviousness.

G. Local Patent Rules

Sun respectfully objects to the Local Patent Rules to the extent that such rules require an early and exhaustive disclosure of Sun's factual and legal bases for Sun's claims of invalidity. The Eastern District of Texas's disclosure requirements, and the limitations on Sun's ability to amend the same, effectively conflict with Rules 8, 9, and 15 (among others) of the Federal Rules of Civil Procedure. These rules respectively (1) provide for liberal pleading requirements, (2) specifically limit the circumstances in which specificity in pleading is required, and (3) require the courts to "freely give leave" to amend pleadings, even during the midst of trial when the amendment "will aid in presenting the merits" without prejudicing an objecting party. *See generally* Fed. R. Civ. P. 8, 9, 15; *see also* Fed. R. Civ. P. 83 ("A local rule must be consistent with . . . federal statutes and rules adopted under 28 U.S.C. §§ 2072 and 2075 . . . ").

Sun further objects to the application of the Local Patent Rules in general, specifically to the extent they seek to limit Sun's right to obtain discovery under the Federal Rules of Civil Procedure, and to the extent they are construed as limiting Sun's statutory rights, including, without limitation, those arising under 35 U.S.C. § 282 (requiring a party asserting non-

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infringement or invalidity defenses to provide notice of relevant prior art thirty days before trial). Accordingly, and without waiver of any rights, Sun reserves the right to challenge the application of the Local Patent Rules generally, in whole or in part.

III. OVERVIEW OF THE ASSERTED PATENTS

A. U.S. Patent No. 11,406,598 ("the '598 Patent")

The '598 Patent issued on August 9, 2022, from Appl. No. 17/025,881 ("the '881 application") filed on September 18, 2020, and published on March 25, 2021, as US 2021/0085608 A1. On its face, the '881 application claims the benefit of U.S. Provisional Patent Application No. 62/903,511 ("the '511 application"), filed on September 20, 2019.

1. Claims of the '598 Patent

The '598 Patent issued with fifteen claims. One independent claim and fourteen dependent claims are provided below.

> 1. A method of producing a storage-stable form of lyophilized amorphous phenobarbital sodium composition, comprising:
>
> adding phenobarbital sodium to water to form a phenobarbital sodium solution having a pH of between 9.2 and 10.2, wherein the phenobarbital sodium solution does not contain an organic solvent, and wherein the phenobarbital sodium solution optionally further comprises sodium chloride;
>
> lyophilizing the phenobarbital sodium solution in a container under a protocol comprising a freezing step, a primary drying step, and a secondary drying step to thereby produce the lyophilized amorphous phenobarbital sodium composition;
>
> wherein the freezing step comprises freezing the lyophilized amorphous phenobarbital sodium to a temperature of about −50° C. without application of vacuum;
>
> wherein the primary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about −50° C. and about 0° C. for at duration of at least 1,000 minutes;

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wherein the secondary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about 25° C. and about 50° C. for at duration of at least 200 minutes;

wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.5%; and

wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

2. The method of claim 1, wherein the sodium chloride is present in the phenobarbital sodium solution in an amount that, upon reconstitution of the lyophilized amorphous phenobarbital sodium in the aqueous solution, yields a sodium chloride concentration of 0.9% in the reconstituted solution.

3. The method of claim 1, wherein the phenobarbital sodium solution in the container is present in an amount of about 65 mg, or about 100 mg, or about 130 mg, or about 200 mg.

4. The method of claim 1, wherein the water is sparged with nitrogen.

5. The method of claim 1, wherein the phenobarbital sodium solution does not contain a preservative.

6. The method of claim 1, wherein the primary drying step is performed using at increasing temperatures that increase from about −50° C. to about 0° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg.

7. The method of claim 1, wherein the primary drying step is performed using at constant temperature of about −42° C. when the amount of phenobarbital sodium in the container is 200 mg.

8. The method of claim 1, wherein the secondary drying step is performed using at decreasing temperatures that decrease from about 50° C. to about 25° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg.

9. The method of claim 1, wherein the secondary drying step is performed using at constant temperature of about 35° C. when the amount of phenobarbital sodium in the container is 200 mg.

10. The method of claim 1, wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.2%.

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11. The method of claim 1, wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.0%.

12. The method of claim 1, wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

13. The method of claim 1, wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no detectable quantities of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution.

14. The method of claim 1, wherein the storage is at 40° C. and 75% relative humidity.

15. The method of claim 1, wherein the lyophilized amorphous phenobarbital sodium composition contains at least 98% lyophilized amorphous phenobarbital sodium.

2. Prosecution History of the '598 Patent

The Examiner rejected the originally filed claim 1 as being anticipated by U.S. Patent Application Publication No. 2010/0035904 A1 ("Sun '094") and claims 16-20 as being anticipated by or, in the alternative, as being obvious over Lynne Kelly et al., *Phenobarbital Sodium*, CRITICAL CARE TRAUMA CENTRE ("Kelly"). Office Action for Appl. No. 17/025,881 dated Nov. 30, 2020. The Examiner further rejected pending claims 2, 6, 8-13, and 15 as being obvious over Sun '094, in view of Meg Snyder, *Lyophilization: The basics*, DRUG DISCOVERY & DEVELOPMENT (Mar. 7, 2017) ("Snyder") and Nancy J. Dietz et al., *Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs*, 5(12) PHARM. RES. 803 (1988) ("Dietz"). *Id.* Pending claims 3-5, 7, and 14 were also rejected as being obvious over Sun '094, in view of Snyder, Dietz, and U.S. Patent No. 6,077,545 ("Roskos"). *Id.*

In response, the Applicant amended pending independent claims 1, 2, and 16 to "clarify that lyophilized amorphous Phenobarbital Sodium is provided in a storage-stable form that forms

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no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution" and argued, *inter alia*, that these limitations are not taught or suggested by the cited references. Response to Office Action for Appl. No. 17/025,881 dated Feb. 12, 2021.

Finding the Applicant's arguments to be unpersuasive, the Examiner once again rejected pending claim 1 as being anticipated by Sun '094. Office Action for Appl. No. 17/025,881 dated Feb. 26, 2021. The Examiner found that the "new limitations" from the Applicant's amendments were inherent properties and were necessarily present in the prior art. *Id.* The Examiner further rejected pending claims 2, 6, 8-13, 15, and 21-22 as being obvious over Sun '094, in view of U.S. Patent Application Publication No. US 2017/0143719 ("Parker") and Snyder, finding that Parker is directed to stable formulation of phenobarbital sodium injection that do not generate impurities including phenylethylacetylurea (PEAU) and phenyl butyric acid (PBA). *Id.* The Examiner also rejected pending claims 3-5, 7, and 14 as being obvious over Sun '094, in view of Parker, Snyder, and Roskos, and pending claims 16-20 as being obvious over Kelly and Sun '094.

In response, the Applicant amended pending independent claims 1, 2, and 16, along with their respective dependent claims 3, 8-12, 14, 15, 22, and 23 to "clarify that lyophilized amorphous Phenobarbital Sodium is provided in a storage-stable <u>powder</u> form" and argued, *inter alia*, that these limitations are not taught or suggested by the cited references. Response to Final Office Action for Appl. No. 17/025,881 dated May 13, 2021. The Applicant further distinguished Parker as a liquid solution form of Phenobarbital Sodium. *Id.* The Applicant also submitted a declaration from Dr. Dasaradhi Lakakraju, the Chief Scientific Officer at Nivagen Pharmaceuticals Inc., stating that "Phenobarbital Sodium in a liquid solution form behaves very differently during storage as compared to the Phenobarbital Sodium in a lyophilized amorphous powder form" and that "[a] liquid solution form allows the chemical processes of degradation of

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Phenobarbital Sodium and formation of PEAU to continue throughout the storage duration, which is not the case with the dry powder form of the composition." Declaration of Dr. Dasaradhi Lakakraju Under 37 C.F.R. § 1.132 for Appl. No. 17/025,881 dated May 13, 2021. Dr. Lakakraju further stated that "[l]yophilization is a general term for water removal from a composition via sublimation, and numerous process parameters such as temperatures, temperature gradients, degree of vacuum applied, and/or time periods at specific temperatures and partial vacuum can significantly affect the physicochemical properties of the lyophilized product." *Id.*

Finding Applicant's and Dr. Lakakraju's arguments unpersuasive, the Examiner again raised obviousness rejections. Office Action for Appl. No. 17/025,881 dated June 1, 2021. The Examiner further noted that "crystalline form [of phenobarbital sodium] is not the claimed subject matter," and thus, "the property of crystalline form is irrelevant" and that "the claimed pharmaceutical composition and methods of making thereof do NOT have any [lyophilization] parameters, except pH which was taught by Parker." *Id.* Following a telephonic interview conducted on August 24, 2021, the Applicant again amended its claims, including manufacturing steps and narrowing the range of pH, and requested allowance of all pending claims. Response to Non-Final Office Action for Appl. No. 17/025,881 dated Aug. 24, 2021.

On August 31, 2021, a third party submitted a Third Party Submission of Prior Art for consideration and entry, identifying twenty prior art references and a claim chart showing the relevance of the cited references. Third-Party Submission of Prior Art Under 37 C.F.R. § 1.290. The Examiner found the third-party submission to be compliant with 35 U.S.C. § 122(e) and 37 C.F.R. § 1.290 and allowed the submission to be entered in the application. Office Action for Appl. No. 17/025,881 dated Sept. 2, 2021.

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Based on the Applicant's amendment, the Examiner again rejected pending claims 1-2, 8-13, 15, and 21-27 as being obvious over Parker, in view of *Lyophilization of Parenteral (7/93): Guide to Inspection of Lyophilization of Parenterals*, U.S. FOOD AND DRUG ADMINISTRATION (1993), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793 ("FDA_7/93") and claims 4-7 and 14 as being obvious over Parker, in view of FDA_7/93 and Roskos. Office Action for Appl. No. 17/025,881 dated Sept. 23, 2021. Regarding the claimed amounts of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG), the Examiner found that these are considered "properties of the lyophilized Phenobarbital sodium." *Id.* Moreover, although Parker discusses using further components of the liquid solution such as C1-C4 alcohol and propylene glycol, the Examiner noted that the pending claim's transition phrase "comprising" allowed the presence of unrecited ingredients. *Id.*

In response, the Applicant cancelled pending claims 1-27 and added new claims 28-47. Response to Final Office Action for Appl. No. 17/025,881 dated Dec. 22, 2021. The Applicant distinguished Parker from the pending claims, noting that Parker uses organic solvents, specifically C1-C4 alcohols and glycols, in place of water. *Id.* In contrast, the pending claims require the phenobarbital sodium compositions to be "free of organic solvents." *Id.* Furthermore, the Applicant noted that the solvent system of Parker is unsuitable for producing a lyophilized phenobarbital sodium because the alcohol/glycol mixtures will not sublimate and desorb. *Id.*

On February 8, 2022, the Examiner issued a Restriction Requirement noting as follows:

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 28-42, drawn to a method of producing, classified in A1K 9/19.

II. Claims 43-47, drawn to pharmaceutical composition, classified in A61K 31/515.

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Office Action for Appl. No. 17/025,881 dated Feb. 8, 2022. The Applicant thereafter elected Group I (reading on claims 28-42). Response to Restriction Requirement for Appl. No. 17/025,881 dated Mar. 9, 2022. The Applicant also amended claims 28, 39, and 40 to include a new limitation of "at least 24 months at room temperature" "to even more clearly point to the unexpected benefits of the claimed method." *Id.*

During an Examiner-initiated interview on March 15, 2022, the obviousness rejections based on Parker were withdrawn in view of Parker's "inclusion of organic solvents." Examiner-Initiated Interview Summary for Appl. No. 17/025,881 dated Mar. 30, 2022; *see also* Notice of Allowance and Fee(s) Due for Appl. No. 17/025,881 dated Mar. 30, 2022 ("The prior art neither teaches, nor fairly suggests the instantly claimed method of making a lyophilized sodium phenobarbital. The closest prior art is that of Parker (US 2017/0143719), which includes organic solvents which are excluded by the instantly claimed method."). The Examiner also noted that the new claim limitation of "at least 24 months at room temperature" was "based on a statement of equivalence with extreme conditions for 6 months, but has no support from any data" and that the original claim limitation of 3 month was restored. Examiner-Initiated Interview Summary for Appl. No. 17/025,881 dated Mar. 30, 2022.

3. Disclosure of the '598 Patent

The '598 Patent discloses "compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water." '598 Patent at 1:12-15. As described in the Detailed Description section, phenobarbital sodium has an IUPAC (International Union of Pure and Applied Chemistry) name of "sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$." *Id.* at 8:7-13.

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In the Background section, the '598 Patent describes prior art compositions of phenobarbital sodium. *Id.* at 1:34-2:33. The '598 Patent indicates that "Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic" and that it is "typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent." *Id.* at 1:34-43 (citing Parker, which is "a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol"). The '598 Patent notes the stability of solubilized phenobarbital sodium as a "recurring problem" as it "readily hydrolyzes in water forming various [toxic] degradation products," including "Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG)." *Id.* at 1:44-63. The '598 Patent describes previous efforts to decrease the formation of toxic degradation products in the phenobarbital sodium formulations, including Parker, which "focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products," but "impurities [in Parker's liquid formulation] such a PEAU are still present in undesirable amounts, particularly after extended storage." *Id.* at 1:64-2:16.

The '598 Patent indicates that the present invention provides compositions of and methods of producing "amorphous lyophilized Phenobarbital Sodium with high stability and purity," disclosing that the lyophilized composition may include "no less than 98% Phenobarbital Sodium" and that the amorphous composition is "a storage-stable form of lyophilized Phenobarbital Sodium." *Id.* at 2:37-44. The '598 Patent states that the "[t]he quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are

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less than those in current commercial products" and that "the stability of this formulation is superior to that of current commercial products." *Id.* at 2:47-51.

The '598 Patent discloses that "[p]referably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%" and "[a]lternatively, the percentage of the lyophilized formulation that is amorphous can be 100%." *Id.* at 2:60-64. Moreover, the '598 Patent further states that "the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.)." *Id.* at 2:64-67.

In typical embodiments, the '598 Patent indicates that "the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg" and that it can be administered as "intramuscular injection or intravenous injection." *Id.* at 4:54-60; *see also id.* at 15:51-53.

With regard to the allegedly inventive process for preparing the storage-stable form of lyophilized Phenobarbital Sodium composition, the '598 Patent discloses that the process includes "adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution." *Id.* at 3:7-12; *see also id.* at 8:52-55, 9:14-21. To adjust the pH of the phenobarbital sodium solution, the '598 Patent suggests using hydrochloric acid (HCl) or Sodium Hydroxide (NaOH). *Id.* at 3:21-26, 9:21-25. The '598 Patent also notes that "[i]n preferred embodiments, the Water for Injection is sparged with nitrogen [for at least 30 minutes] prior to adding the Phenobarbital Sodium" and "[i]n additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium." *Id.* at 3:14-21; *see also id.* at 8:55-67. The '598

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Patent further discloses filtering the phenobarbital sodium solution prior to lyophilization. *Id.* at 3:55-58; *see also id.* at 9:26-33.

The lyophilized phenobarbital sodium can be reconstituted in "either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration." *Id.* at 11:20-23. Once the lyophilized phenobarbital sodium has been reconstituted after storage, the '598 Patent discloses that the solution has "no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG." *Id.* at 4:39-43. The '598 Patent further discloses:

> Typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.1% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months both at RT and accelerated stability conditions. More typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.). Additionally, or alternatively, the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and accelerated stability conditions.

Id. at 3:27-43.

In Tables 2 and 3, the '598 Patent compares the disclosed 65 mg and 130 mg lyophilized phenobarbital sodium that was reconstituted in water to the marketed 65 mg and 130 mg liquid phenobarbital sodium for injection USP (Westward Pharmaceuticals):

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TABLE 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder

	Product Name										
	Phenobarbital Sodium for Injection USP, 65 mg/mL (Marketed product)					Phenobarbital Sodium for Injection USP, 65 mg/Vial (Nivagen formulation- NPH1907)					
	Formulation Type										
	Liquid					Lyophilized powder					
	Stability Data										
	3 Months		6 Months			3 Months		6 Months		15 Months	
	RT 25° C.,	ACC 40° C.,	RT 25° C.,	ACC 40° C.,		RT 25° C.,	ACC 40° C.,	RT 25° C.,	ACC 40° C.,	RT** 25° C.,	

TABLE 2-continued

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder

Test	Initial	60% RH	75% RH	60% RH	75% RH	Initial	60% RH	75% RH	60% RH	75% RH	60% RH
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$	$	$	$	$	$	$
pH*	9.3	9.8	9.7	9.6	9.6	9.8	9.6	9.6	9.7	9.7	9.8
% Assay of Phenobarbital Sodium	102.4	97.6	103.1	96.3	86.7	99.1	98.7	97.4	100.0	99.3	96.0
% degradation (Area percent)	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
2EPMM											
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	0.5	1.0	3.7	1.4	5.8	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	BQL	BQL	0.1	BQL	0.3	BQL	BQL	BQL	0.07	0.06	0.04
Total degradation products	0.5	1.0	3.8	1.4	6.1	BQL	BQL	BQL	0.07	0.06	0.04

CCVS: Clear Colorless Viscous Solution;
CCS: Clear Colorless Solution;
WLP: White Lyophilized powder
$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.
BQL: Below Quantitation Limit; (QL-0.05%);
ND: Not Detected
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-phenylbutyrylguanidine,
PEAU: phenylethylacetylurea or Pheneturide
*pH of both liquid and lyophilized formulations are measured at 65 mg/mL concentration
**The samples were stored at 30 ± 2° C., 65% RH ± 5

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TABLE 3

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation

	Product Name										
	Phenobarbital Sodium for Injection USP, 130 mg/mL (Marketed product)					Phenobarbital Sodium for Injection USP, 130 mg/vial (Nivagen formulation-NPH1912)					
	Formulation Type										
	Liquid					Lyophilized powder					
	Stability Data										
		3 Months		6 Months			3 Months		6 Months		15 Months
Test	Initial	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT 25° C., 60% RH	ACC 40° C., 75% RH	Initial	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT** 25° C., 60% RH
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$	$	$	$	$	$	$
pH*	9.5	9.9	9.9	9.8	9.7	9.8	9.8	9.8	9.8	9.8	10.0
% Assay of Phenobarbital Sodium	100.8	95.5	92.9	95.2	90.9	98.3	100.1	97.9	100.2	99.4	98.3
Related Substances (% Area) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND

TABLE 3-continued

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation

PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	0.5	0.9	2.8	1.1	4.3	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	ND	BQL	0.1	BQL	0.4	BQL	BQL	BQL	0.05	0.05	0.04
Total degradation products	0.5	0.9	2.9	1.1	4.7	BQL	BQL	BQL	0.05	0.05	0.04

CCVS: Clear Colorless Viscous Solution;
CCS: Clear Colorless Solution;
WLP: White Lyophilized powder
$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.
BQL: Below Quantitation Limit; (QL-0.05%);
ND: Not Detected
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-phenylbutyrylguanidine,
PEAU: phenylethylacetylurea or Pheneturide
*pH for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution
**The samples were stored at 30 ± 2° C., 65% RH ± 5

Id. at Tables 2 and 3. The '598 Patent notes that "the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration." *Id.* at cols. 13-14.

The '598 Patent also discloses

- the stability data of Phenobarbital Sodium for Injection, 200 mg/vial, reconstituted in 10 mL of Water for Injection (Table 7);
- the stability data of Phenobarbital Sodium for Injection, 200 mg/vial, along with 90 mg of Sodium Chloride reconstituted in 10 mL of Water for Injection (Table 8); and

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- the stability data of Phenobarbital Sodium for Injection, 130 mg/vial, reconstituted in 20 mg/mL of Water for Injection (Table 9):

TABLE 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

		Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
Test	Spec.	Jun. 5, 2020	2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS

TABLE 7-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

		Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
Test	Spec.	Jun. 5, 2020	2-8° C.	RT
pH (20 mg/mL)	9.2-10.2	9.9	9.7	9.8
% Assay Phenobarbital Sodium	90.0-105.0	100.1	100.1	100.1
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.24
Total degradation products	NMT 1.5%	BQL	0.09	0.27
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
Note Book Reference		192045-163 to 189	192045-163-183	

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

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TABLE 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)

			Reconstituted Solution Stability after 20 hrs	
Test	Specification	Initial	2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0-105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5%	BQL	0.09	0.3

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TABLE 8-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)

			Reconstituted Solution Stability after 20 hrs	
Test	Specification	Initial	2-8° C.	RT
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

WLP: White Lyophilized Powder;

CCS: Clear Colorless Solution, 1 minute after reconstitution;

ND: Not Detected;

NMT: Not More Than;

BQL: Below Quantitation Limit (0.05%)

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

PBG: α-Phenylbutyrylguanidine;

PEAU: Phenylethylacetylurea

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TABLE 9

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)

		Time						
	Shelf life		2 hrs		4 hrs		24 hrs	
Tests	Specifications	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.2-10.2	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	90.0%-105.0%	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL
2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PEAU	NMT 0.2%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Any unspecified degradation product @ RRT 0.37								
Total degradation products	NMT 1.5%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	To be reported	158	NP	NP	NP	NP	159	158

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

Id. at Tables 7-9. The '598 Patent also discloses

- six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 10);
- six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 11)[2];
- three months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial (Table 12);
- three months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial (Table 13); and
- six months of stability data for Phenobarbital Sodium for Injection, 100 mg/vial (Table 16).

Id. at Tables 10-13, 16. The room temperature ("RT") and accelerated ("ACC") stability conditions were set at 25°C with 65% relative humidity ("RH") and 40°C with 75% RH, respectively. *Id.*

[2] The Applicant repeated the same six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (as shown in Table 10) for Table 11.

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TABLE 10

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

		Initial	1 Month		3 Months		6 Months	
		DOA:	DOA: Mar. 29, 2020		DOA: May 20, 2020		DOA: Sep. 4, 2020	
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.5	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	301.6	101.5	101.3	100.5	100.0	101.2

TABLE 10-continued

Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.3	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192046-23 to 45		192045-135 to 153		192051-84 to 122	

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

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TABLE 11

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

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

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

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TABLE 12

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch#NPH2031A Fill Volume: 2.1 mL	Date Manufactured: Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear		Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);		Jun. 9, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024		
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay Phenobarbital Sodium	90.0-105.0	100.1	98.1	101.0
Related Substances (% Area)	NMT 0.2%	ND	ND	ND
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.09	0.09
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051-84 to 122	

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

TABLE 13

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch#NPH2031A Fill Volume: 2.1 mL	Date Manufactured: Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear		Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);		Jun. 9, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024		
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6
Related Substances	NMT 0.2%	BQL	ND	ND

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TABLE 13-continued

(% Area) 2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.1	0.08
Water Content by Karl Fischer	NMT 3.0%	0.8	0.9	1.1
Note Book Reference		192045-163 to 189	192051-84 to 122	

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

TABLE 16

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

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

TABLE 16-continued

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

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

Id. at Tables 10-13, 16.

The ’598 Patent further describes lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial, and 200 mg/vial:

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TABLE 15

Lyophilization Cycle parameters.

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

TABLE 15-continued

Lyophilization Cycle parameters.

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

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

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

Id. at Table 15.

B. U.S. Patent No. 11,878,076 ("the '076 Patent")

The '076 Patent issued on January 23, 2024, from Appl. No. 18/100,804 ("the '804 application") filed on January 24, 2023, and published on May 25, 2023, as US 2023/0157959 A1. On its face, the '804 application is a continuation application of U.S. Appl. No. 17/854,914 ("the '914 application"), filed on June 30, 2022, which is a continuation-in-part of the '881 application, which claims the benefit of U.S. Provisional Patent Application No. 62/903,511 ("the '511 application"), filed on September 20, 2019.

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1. Claims of the ’076 Patent

The ’076 Patent issued with twenty claims. Two independent claim and eighteen dependent claims are provided below.

1. A storage stable pharmaceutical product, comprising:

   a single use dose vial, and

   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,

   wherein the composition is sterile and lyophilized, and

   wherein the composition comprises no less than 98% phenobarbital sodium.

2. The pharmaceutical product of claim 1, 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. The pharmaceutical product of claim 1, 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. The pharmaceutical product of claim 1, 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. The pharmaceutical product of claim 1, wherein the composition is amorphous.

6. The pharmaceutical product of claim 1, 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).

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7. A pharmaceutical product, comprising:

   a single use dose vial, and

   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,

   wherein the composition is sterile and lyophilized,

   wherein the composition comprises no less than 98% phenobarbital sodium, and

   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. The pharmaceutical product of claim 7, 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. The pharmaceutical product of claim 7, 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).

10. The pharmaceutical product of claim 7, 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. The pharmaceutical product of claim 10, 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. The pharmaceutical product of claim 7, wherein the composition is amorphous.

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13. The pharmaceutical product of claim 12, 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. The pharmaceutical product of claim 1, 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).

15. The pharmaceutical product of claim 14, wherein the composition is amorphous.

16. The pharmaceutical product of claim 1, wherein the product comprises the 100 mg dose in the single use dose vial.

17. The pharmaceutical product of claim 7, wherein the product comprises the 100 mg dose in the single use dose vial.

18. The pharmaceutical product of claim 8, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

19. The pharmaceutical product of claim 8, 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. The pharmaceutical product of claim 8, wherein the composition is amorphous.

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2. Prosecution History of the ’076 Patent

The Examiner rejected the originally filed claims 1-20 as being obvious over U.S. Patent Application Publication No. US 2017/0143719 (“Parker”) [3] in view of *Lyophilization of Parenteral (7/93): Guide to Inspection of Lyophilization of Parenterals*, U.S. FOOD AND DRUG ADMINISTRATION (1993), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793 (“FDA_7/93”). Office Action for Appl. No. 18/100,804 dated June 23, 2023. The Examiner noted that “it would have been well within the skill of the ordinary practitioner to claim the stable product as taught by Parker, and further to include the water content, humidity, and temperatures of the instant claims as part of the lyophilization product as taught by FDA_7/93, with a reasonable expectation of similar shelf stability.” *Id.*

An Applicant-initiated interview was conducted on September 20, 2023, where the Applicant “pointed out the fact that neither reference points to a concentration of no less than 98%, or the specific conditions necessary to obtain these results” and that “[n]ew claims were proposed setting out these limitations.” Applicant-Initiated Interview Summary for Appl. No. 18/100,804 dated September 25, 2023. Following the telephonic interview, the Applicant cancelled claims 1-20 and proposed new claims 21-33. Response to Office Action for Appl. No. 18/100,804 dated September 20, 2023. Although the Applicant agreed that “Parker is concerned with stability of phenobarbital sodium in an injectable solution containing the phenobarbital sodium and that Parker does not lyophilize its product,” the Applicant argued that Parker does

[3] There appears to be a typo in the citation to Parker within the Office Action. The correct citation to Parker can be found in the Notice of References Cited for Appl. No. 18/100,804 dated June 23, 2023. *See also* Response to Office Action for Appl. No. 18/100,804 dated September 20, 2023.

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not provide a motivation to modify his formulation because "the problem of stability of phenobarbital sodium [in Parker] was already solved." *Id.* Furthermore, the Applicant noted that lyophilization of Parker will not produce a composition that "comprises no less than 98% phenobarbital sodium" because "Parker uses in his formulations a number of stabilizing co-solvents such as glycols (*e.g.*, propylene glycol) and C1-C4 alcohols (*e.g.*, ethanol) in quantities that exceed the amount of phenobarbital sodium" and because glycols, which are "not volatile under lyophilization conditions," will remain in the lyophilization vial together with the phenobarbital sodium. *Id.* Finally, the Applicant contended that "there is a wide range of lyophilization processes and lyophilization conditions (*e.g.*, temperature, pressure, time at the temperature and/or pressure for each of the freezing, primary and secondary drying steps) that will lead to a wide range of physicochemical parameters of the lyophilized product" and that "FDA_7/93 fails to provide any guidance as to what lyophilization processes and lyophilization conditions should be chosen to arrive at the lyophilized product as presently claimed." *Id.*

The Examiner then allowed pending claims 21-33 to issue, finding that "neither the Parker reference, nor the FDA_7/93 reference teach the amount of phenobarbital, the reaction conditions to form it, or its amorphous property." Notice of Allowance and Fee(s) Due for Appl. No. 18/100,804 dated Oct. 16, 2023. Following the Notice of Allowability, the Applicant submitted an amendment under 37 C.F.R. § 1.312 to add further claims, which were "combinations of allowed dependent . . . or merely narrow[ed] the [allowed] independent claims." Amendment Under 37 CFR § 1.312 ('Rule 312 Amendment') for Appl. No. 18/100,804 dated Nov. 22, 2023. After the amendment was considered and entered into the application, the

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Examiner then allowed pending claims 21-40 to issue. Corrected Notice of Allowability for Appl. No. 18/100,804 dated Dec. 15, 2023.[4]

3. Disclosure of the ’076 Patent

The ’076 Patent specification encompasses the disclosures of the ’598 patent. *See supra* Section III.A.3. The Applicant *replaced* Table 11 with twenty-four months of stability data for Phenobarbital Sodium for Injection, 130 mg/vial, and Table 13 with twelve months of stability data for Phenobarbital Sodium for Injection, 130 mg/vial:

[4] Although the Corrected Notice of Allowability for Appl. No. 18/100,804 dated Dec. 15, 2023, states that the allowed claims are 1-40, the issued ’076 Patent contains twenty claims.

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TABLE 11

Product Name Phenobarbital Sodium for Injection USP, 130 mg/vial
Batch#NPH2021 Fill Volume: 1.05 mL Date Manufactured: Jan. 20, 2020
Vial Make 2 mL Clear Glass Vial Date Initiated: Feb. 14, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, Re test Date: Nov. 16, 2023
Stopper Used 13 mm Grey Rubber stopper Flip Off Seals: 13 mm Plastic with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	1 Month DOA: Mar. 23, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020		24 Months DOA: 18 Mar. 2022
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099- 157, 159, 167, 170

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

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TABLE 13

Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial) Batch#NPH2031B Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020
Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV Re test Date: Jul. 20, 2024
Stopper Used 20 mm Lyophilization Rubber stopper Flip Off Seals:
20 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	3 Months		6 Months		12 months
		DOA:	DOA: Sep. 4, 2020		DOA: Dec. 11, 2020		DOA: 11 Apr. 2022
Test	Spec.	Jun. 5, 2020	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area)	NMT 0.2%	BQL	ND	ND	ND	ND	ND
2EPMM							
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137

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

'076 Patent at Tables 11, 13.

The '076 Patent further presents "extended stability studies" of lyophilized amorphous phenobarbital sodium, demonstrating "a storage stability at 25° C. and 60% relative humidity for up to and beyond three years," with the composition readily dissolving upon reconstitution. '076 Patent at 29:61-30:59. The '076 Patent discloses:

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- 24 months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 18);
- 37 months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 19);
- 30 months of stability data for Phenobarbital Sodium for Injection, 100 mg/vial (Table 20);
- 37 months of stability data for Phenobarbital Sodium for Injection, 130 mg/vial (Table 21);
- 24 months of stability data for Phenobarbital Sodium for Injection, 130 mg/vial (Table 22);
- 22 months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial (Table 22)[5]; and
- 12 months of stability data for Phenobarbital Sodium for Injection with 9% saline/vial, 200 mg/vial (Table 23).

Id. at Tables 18-23. The room temperature ("RT") and accelerated ("ACC") stability conditions were set at 25°C with 65% relative humidity ("RH") and 40°C with 75% RH, respectively. *Id.*

[5] The '076 Patent includes Table 22 twice with different data: one table displays 24 months of stability data for Phenobarbital Sodium for Injection, 130 mg/vial, and the other presents 22 months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial. Additionally, the second Table 22 contains a typo, as April 11, 2022 is approximately 22 months after the initial date of June 5, 2020, not "11 months."

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TABLE 18

(65 mg/vial, up to 24 months)
Product Name Phenobarbital Sodium for Injection USP, 65 mg/vial Batch#NPH2020
Fill Volume: 1.05 mL Date Manufactured: Jan. 20, 2020
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 14, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper Flip Off Seals:
13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	1 Month DOA: Mar. 23, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020		24 Month DOA: 18 Mar. 2022
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6	9.7
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.3	100.0	101.2	101.2
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.9	1.3	1.4	1.5	1.6	2.1	1.8
Note Book Reference		192039-150 to 158	192045-23 to 45		192045-135 to 151		192051-84 to 122		192099-157, 159, 167, 170

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

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TABLE 19

(65 mg/vial, up to 37 months)
Product Name Phenobarbital Sodium for Injection USP, 65 mg/vial Batch#NPH1907 Date Manufactured: Feb. 21, 2019
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 25, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C. ± 2° C., 60% RH ± 5% (RT) & 40° C., ± 2° C., 75% RH ± 5% (ACC)

		Initial	1 Month		3 Months		6 Months		15 Months	37
		DOA:	DOA: Mar. 28, 2019		DOA: May 24, 2019		DOA: Aug . 28, 2019		DOA: Jun. 12, 2020	Months
Test	Spec.	Feb. 25, 2019	RT	ACC	RT	ACC	RT	ACC	*RT	**RT
Description	White to almost white lyophilized powder	+	+	+	+	+	+	+	+	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (65 mg/mL)	9.2-10.2	9.8	10.0	10.1	9.6	9.6	9.7	9.7	9.8	
% Assay Phenobarbital Sodium	90.0%-105.0%	99.1	98.4	99.1	98.7	97.4	100.0	99.3	96.0	

TABLE 19-continued

(65 mg/vial, up to 37 months)
Product Name Phenobarbital Sodium for Injection USP, 65 mg/vial Batch#NPH1907 Date Manufactured: Feb. 21, 2019
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 25, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C. ± 2° C., 60% RH ± 5% (RT) & 40° C., ± 2° C., 75% RH ± 5% (ACC)

		Initial	1 Month		3 Months		6 Months		15 Months	37
		DOA:	DOA: Mar. 28, 2019		DOA: May 24, 2019		DOA: Aug . 28, 2019		DOA: Jun. 12, 2020	Months
Test	Spec.	Feb. 25, 2019	RT	ACC	RT	ACC	RT	ACC	*RT	**RT
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Water Content by Karl Fischer	NMT 3.0%	0.8	1.1	1.3	1.6	1.7	1.2	2.2	2.0	
Note Book Reference		192019-41, 44, 45, 47	192019-122, 123, 126, 127		192025-25, 30, 31, 34		192031-8, 12, 14, 16, 17, 18		192051-2 to 11	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea;
*The samples were stored at 30° C. ± 2° C. 65% (RH) ± 5%;
**The samples were moved from 30° C. ± 2° C. 65% (RH) ± 5% and stored at 25° C. ± 2° C. 60% (RH) ± 5% at 15 month time point.

TABLE 20

(100 mg/vial, up to 30 months)
Product Name Phenobarbital Sodium for Injection USP, 100 mg/vial
Batch#NPH1980 Fill Volume: 1.0 mL Date Manufactured: Sep. 25, 2019
Vial Make 5mL Clear Untreated 5 mL Clear Treated Date Initiated: Sep. 30, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal Lot# NA
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial		1 Month DOA: Oct. 31, 2019				3 Months DOA: Jan. 10, 2020			
		DOA: Sep. 27, 2019		RT		ACC		RT		ACC	
Test	Spec.	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7
% Assay of Phenobarbital	90.0%-105.0%	98.4	97.8	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT0.37	NMT 0.2%	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL

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TABLE 20-continued

(100 mg/vial, up to 30 months)
Product Name Phenobarbital Sodium for Injection USP, 100 mg/vial
Batch#NPH1980 Fill Volume: 1.0 mL Date Manufactured: Sep. 25, 2019
Vial Make 5mL Clear Untreated 5 mL Clear Treated Date Initiated: Sep. 30, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal Lot# NA
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

Total Impurities	NMT 1.5%	0.05	0.08	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.6	1.0	0.9	1.1	1.1	1.2	1.1	1.5	1.4
Note Book Reference		192031-91 to 101			192031-169 to 183				192039-44 to 52		

			6 Months DOA: Apr. 8, 2020				30 Months DOA: 18 Mar. 2022	
			RT		ACC		RT	
Test		Spec.	UT	T	UT	T	UT	T
Description		WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance		CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)		9.2-10.2	9.8	9.9	9.8	9.9	9.6	9.6
% Assay of Phenobarbital		90.0%-105.0%	97.7	98.3	97.2	97.6	99.2	100.0
% Impurity 2EPMM		NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
PBG		NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU		NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT0.37		NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities		NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer		NMT 4.0%	1.6	1.2	1.5	2.0	2.1	1.8
Note Book Reference				192045-46 to 85			192039-157, 159, 167, 170157, 159, 167, 170	

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

TABLE 21

(130 mg/vial, up to 37 months)
Product Name Phenobarbital Sodium for Injection USP, 130 mg/vial Batch#NPH1912 Date Manufactured: Feb. 23, 2019
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 25, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C. ± 2° C., 60% RH ± 5% (RT) & 40° C., ± 2° C., 75% RH ± 5% (ACC)

		Initial	1 Month DOA: Mar. 28, 2019		3 Months DOA: May 24, 2019	
Test	Spec.	DOA: Feb. 28, 2019	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS

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TABLE 21-continued

(130 mg/vial, up to 37 months)
Product Name Phenobarbital Sodium for Injection USP, 130 mg/vial Batch#NPH1912 Date Manufactured: Feb. 23, 2019
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 25, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C. ± 2° C., 60% RH ± 5% (RT) & 40° C., ± 2° C., 75% RH ± 5% (ACC)

pH (100 mg/mL)	9.2-10.2	9.8	10.0	9.9	9.8	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	98.3	97.1	98.3	100.1	97.9
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL
Total Degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.6	1.1	1.2	1.1	1.3
Note Book Reference		192019-41, 44, 45, 47	192019-132, 123, 125, 126		192025-24, 30, 31, 34	

		6 Months DOA: Aug. 28, 2019		15 Months DOA: Jun. 12, 2020	37 Months DOA: 18 Mar. 2022
Test	Spec.	RT	ACC	RT	RT
Description	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.8	9.8	10.0	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	98.8	99.4	98.3	99.2
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	0.05	BQL	BQL
Total Degradation products	NMT 1.5%	BQL	0.05	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	1.9	1.4	1.4	1.5
Note Book Reference		192031-8, 12, 14, 16, 17, 18		192051-2 to 11	192099-157, 159, 167, 170

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

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TABLE 22

(130 mg/vial, up to 24 months)
Product Name Phenobarbital Sodium for Injection USP, 130 mg/vial
Batch#NPH2021 Fill Volume: 1.05 mL Date Manufactured: Jan. 20, 2020
Vial Make 2 mL Fiolax Clear Blow Back Vial Date Initiated: Feb. 14, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper
Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	1 Month DOA: Mar. 23, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020		24 Months DOA: 18 Mar. 2022
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099-157, 159, 167, 170

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

TABLE 22

(200 mg/vial, up to 22 months)
Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial
Batch#NPH2031A Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020
Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	3 Months DOA: Sep. 4, 2020		6 months DOA: Dec. 11, 2020		11 mouths DOA: 11 Apr. 2022
Test	Spec.	DOA: Jun. 5, 2020	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7	9.7	9.7	9.5

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TABLE 22-continued

(200 mg/vial, up to 22 months)
Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial
Batch#NPH2031A Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020
Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:
Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	3 Months DOA: Sep. 4, 2020		6 months DOA: Dec. 11, 2020		11 mouths DOA: 11 Apr. 2022
Test	Spec.	DOA: Jun. 5, 2020	RT	ACC	RT	ACC	RT
% Assay Phenobarbital Sodium	90.0-105.0	100.1	98.1	101.0	100.8	102.5	98.2
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND
2EPMM							
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.05	(BQL)
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3	1.2	1.6	1.5
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137

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

TABLE 23

(200 mg/vial, up to 12 months)
Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial) Batch#NPH2031B Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020
Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020
API Mfg. Phenobarbital Solution, USP Grade P, C-IV:
Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	3 Months DOA: Sep. 4, 2020		6 Months DOA: Dec. 11, 2020		12 months DOA: 11 Apr. 2022
Test	Spec.	DOA: Jun. 5, 2020	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area)	NMT 0.2%	BQL	ND	ND	ND	ND	ND
2EPMM							
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.10	BQL

TABLE 23-continued

(200 mg/vial, up to 12 months)
Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial) Batch#NPH2031B Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020
Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020
API Mfg. Phenobarbital Solution, USP Grade P, C-IV:
Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	3 Months DOA: Sep. 4, 2020		6 Months DOA: Dec. 11, 2020		12 months DOA: 11 Apr. 2022
Test	Spec.	DOA: Jun. 5, 2020	RT	ACC	RT	ACC	RT
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192867-78 to 88		192034-137

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

Id. at Tables 18-23.

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The ’076 Patent further discloses stability data for phenobarbital sodium reconstituted with dextrose, saline, and water:

- 24 hours of stability data for Phenobarbital Sodium for Injection, 65 mg/vial, reconstituted to 1 mg/mL in 5% dextrose (Table 24);
- 24 hours of stability data for Phenobarbital Sodium for Injection, 65 mg/vial, reconstituted to 1 mg/mL in 0.9% saline (Table 25);
- 24 hours of stability data for Phenobarbital Sodium for Injection, 130 mg/vial, reconstituted to 20 mg/mL in 0.9% saline (Table 26);
- 24 hours of stability data for Phenobarbital Sodium for Injection, 130 mg/vial, reconstituted to 20 mg/mL in 5% saline (Table 27); and
- 24 hours of stability data for Phenobarbital Sodium for Injection, 130 mg/vial, reconstituted to 20 mg/mL in water (Table 28).

TABLE 24

(65 mg/vial, reconstituted to 1 mg/ml in 5% dextrose, up to 24 hrs)
Admixture Study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPB2020) (1 mg/mL dilution in 5% Dextrose)

			Time											
			1 hr		2.5 hr		4 hrs		6 hrs		9 hrs		24 hrs	
Specifications	Tests	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Complies	Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1 mg/mL dilution)	8.8	8.8	8.8	8.8	8.8	8.8	8.7	8.8	8.7	8.7	8.7	8.7	8.5
Assay 90%-105%	Assay of Phenobarbital Sodium	95.4	95.7	95.6	95.9	95.4	95.9	97.1	95.6	95.9	94.6	97.1	95.1	96.1
2EPMM NMT0.2%	Related Substances (% Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PEG NMT0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT0.2%	PEAU	ND	ND	BQL	BQL	BQL	ND	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product	Any unspecified degradation product @ RRT 0.29	ND	ND	BDL	ND	BDL	ND	BDL	ND	0.02	BDL	0.02	BDL	0.03
NMT 0.2%	Any unspecified degradation product @ RRT 0.37	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.03	0.02	0.05

TABLE 24-continued

(65 mg/vial, reconstituted to 1 mg/ml in 5% dextrose, up to 24 hrs)
Admixture Study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPB2020) (1 mg/mL dilution in 5% Dextrose)

			Time											
			1 hr		2.5 hr		4 hrs		6 hrs		9 hrs		24 hrs	
Specifications	Tests	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Osmolality To be reported	Osmolality (mOsmol/Kg)	254	NP	Np	NP	NP	NP	NP	NP	NP	NP	NP	255	253
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.08

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

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TABLE 25

(65 mg/vial, reconstituted to 1 mg/ml in 0.9% saline, up to 24 hrs)

		Admixture study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2020) (1 mg/mL) dilution in 0.9% Saline)												
			Time											
			1 hr		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs	
Specifications	Test	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Complies	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1 mg/mL dilution)	9.0	8.8	8.9	9.0	9.0	8.9	8.9	8.9	8.9	8.7	8.8	8.5	8.4
Assay 90%-105%	Assay of Phenobarbital Sodium	95.8	96	94.3	95.4	93.6	95.5	95.2	95.8	93.9	94.6	96.4	95.2	95.3
2EPMM NMT 0.2%	Related Substances (% Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT 0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT 0.2%	PEAU	BQL	ND	BQL	BQL	BQL	BQL	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @ RRT 0.29	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
	Any unspecified degradation product @ RRT 0.037	0.02	0.02	0.03	0.02	0.03	0.02	0.04	0.02	0.04	0.03	0.05	0.03	0.1
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	0.1
Osmolality To be reported	Osmolality (mOsmol/Kg)	288	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	286	287

CCS: Clear colorless solution;
ND: Not detected;
BQL: Below Quantitation limit;
NP: Not performed;
2EPMM: 2-ethylphenylmalonamide monohydrate;
PBG: Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea
BQL: Below Quantitation limit (0.05%)

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TABLE 26

(130 mg/vial, reconstituted to 20 mg/ml in 0.9% saline, up to 24 hrs)
Admixture study of Phenobarbital Sodium for Injection USP,
130 mg/vial (NPH2030) (20 mg/mL dilution In 0.9% Saline)

	Time						
		30 min		90 min		240 min	
Tests	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.3	9.4	9.4
Assay of Phenobarbital Sodium	104.1	103.6	102.4	103.3	102.7	103.2	102.9
Related Substances (% Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	BQL	0.03	0.04	0.03	0.05	0.03	0.07
Total degradation products	BQL	0.03	0.04	0.03	0.05	0.03	0.07
Osmolality (mOsmol/Kg)	418	NP	NP	NP	NP	NP	NP

	Time					
	6 hrs		9.5 hrs		24 hrs	
Tests	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.4	9.2	9.4	9.3
Assay of Phenobarbital Sodium	103.4	102.9	99.5	103.3	103.3	101.3
Related Substances (% Area) 2EPMM	ND	BQL	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.03	0.09	0.03	0.13	0.04	0.24
Total degradation products	0.03	0.09	0.03	0.13	0.04	0.24
Osmolality (mOsmol/Kg)	NP	NP	420	418	417	419

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

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TABLE 27

(130 mg/vial, reconstituted to 20 mg/ml in 5% saline, up to 24 hrs)
Admixture study of Phenobarbital Sodium for Injection USP,
130 mg/vial (NPH2030) (20 mg/mL dilution In 5% Dextrose)

	Time						
		30 min		90 min		4 hrs	
Test	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.4	9.4	9.3
Assay of Phenobarbital Sodium	101	102	100	101.5	102	100.9	101.1
Related Substances (% Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.03	0.03	0.04	0.03	0.06
Total degradation products	0.02	0.02	0.03	0.03	0.04	0.03	0.06
Osmolality (mOsmol/Kg)	379	NP	NP	NP	NP	NP	NP

	Time					
	6 hrs		9.5 hrs		14 hrs	
Test	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.3	9.3	9.4	9.3	9.4	9.4
Assay of Phenobarbital Sodium	101.7	101.6	101.6	102.1	102.4	102.2
Related Substances (% Area) 2EPMM	ND	ND	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.03	0.08	0.03	0.11	0.04	0.19
Total degradation products	0.03	0.08	0.03	0.11	0.04	0.19
Osmolality (mOsmol/Kg)	NP	NP	379	380	377	379

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

TABLE 28

(130 mg/vial, reconstituted to 20 mg/ml in water, up to 24 hrs)
Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030)
(20 mg/mL dilution In Water)

	Time						
		2 hrs		4 hrs		24 hrs	
Tests	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.5	9.5	9.6	9.6	9.5	9.6	9.5

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TABLE 28-continued

(130 mg/vial, reconstituted to 20 mg/ml in water, up to 24 hrs)
Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030)
(20 mg/mL dilution In Water)

	Time						
		2 hrs		4 hrs		24 hrs	
Tests	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Assay of Phenobarbital Sodium	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (% Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	158	NP	NP	NP	NP	159	158

CCS: Clear colourless solution;

ND: Not detected;

BQL: Below Quantitation limit;

NP: Not performed;

2EPMM: 2-ethylphenylmalonamide monohydrate;

PBG: Phenylbutyrylguanidine;

PEAU: Phenylethylacetylurea

Id. at Tables 24-28.

In further experiments, the inventors of the ’076 Patent “investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents,” testing “isopropanol, tert-butanol, ethanol, and acetonitrile as co-solvents” with the concentration of the organic co-solvent being as high as 90%. *Id.* at 51:30-52:35. The ’076 Patent further describes lyophilization cycle parameters used:

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TABLE 30

Lyophilization protocol

Section	Phase	Hold Time [mm]	Temperature ° C.	Vacuum [mTorr]
1	Loading	n.a.	5	off
2	Freezing	5	−5	off
3	Freezing	60	−50	off

TABLE 30-continued

Lyophilization protocol

Section	Phase	Hold Time [mm]	Temperature ° C.	Vacuum [mTorr]
4	Freezing	30	−10	off
5	Freezing	120	−50	off
6	Evacuation	30	−50	75
7	Primary drying	400	−50	75
8	Primary drying	350	−45	75
9	Primary drying	300	−43	75
10	Primary drying	250	−35	75
11	Primary drying	60	−20	75
12	Primary drying	120	0	75
13	Secondary drying	120	50	75
14	Secondary drying	120	25	75

Id. at Table 30. The ’076 Patent discloses:

- 3 months of stability data for 65 mg/vial and 130 mg/vial Phenobarbital Sodium (from a bulk solution containing 5% tert-butanol) (Table 31);
- 3 months of stability data for 65 mg/vial and 130 mg/vial Phenobarbital Sodium (from a bulk solution containing 5% isopropanol) (Table 32); and
- Initial stability data for 65 mg/vial and 130 mg/vial Phenobarbital Sodium from respective bulk solutions containing ethanol or acetonitrile as co-solvents (Table 33).

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TABLE 31

(65/130 mg/vial, 5% tert-butanol, up to 3 months)
Product Name Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution
prepared in 5% Tertiary Butanol Date Manufactured: Feb. 21, 2019 Date Initiated: Sep. 5, 2019
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		NPH1965 (65 mg/vial)			NPH1967 (130 mg/vial)		
		Initial	3 Months DOA: Dec. 20, 2019		Initial	3 Months DOA: Dec. 20, 2019	
Test	Spec.	DOA: Sep. 7, 2019	RT	ACC	DOA: Dec. 20, 2019	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.7	9.7	9.7	9.8	9.8	9.8
pH (100 mg/mL) for 130 mg/vial strength							
% Assay Phenobarbital Sodium	90.0%-105%	98.2	98.8	97.7	100.0	99.9	99.9
Related Substances	NMT 0.2%	ND	ND	ND	ND	ND	ND
2EPMM							
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any other degradation product	NMT 0.2%	0.09	BQL	BQL	0.09	BQL	BQL
Total degradation products	NMT 1.5%	0.09	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.4	NT	NP	0.3	NP	NP
% Residual Solvent (Tertiary butanol)	To be reported	1.2	0.6	0.8	4.4	2.9	1.7
Note Book Reference		192031-46 to 52	192039-9 to 23		192031-46 to 52	192039-9 to 23	

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

TABLE 32

(65/130 mg/vial, 5% isopropanol, up to 3 months)
Product Name Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution
prepared in 5% Isopropanol Date Manufactured: Feb. 21, 2019 Date Initiated: Sep. 5, 2019
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		NPH1966 (65 mg/vial)			NPH1968 (130 mg/vial)		
		Initial	3 Months DOA: Dec. 20, 2019		Initial	3 Months DOA: Dec. 29, 2019	
Test	Spec.	DOA: Sep. 7, 2019	RT	ACC	DOA: Sep. 7, 2019	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.6	9.6	9.7	9.8	9.7	9.7
pH (100 mg/mL) for 130 mg/vial strength							
% Assay Phenobarbital Sodium	90.0%-105%	99.7	98.8	100.0	100.0	101.1	99.1
Related Substances	NMT 0.2%	ND	ND	ND	ND	ND	ND
2EPMM							
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any other degradation product	NMT 0.2%	0.08	BQL	BQL	0.09	BQL	BQL
Total degradation products	NMT 1.5%	0.08	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.3	NP	NP	0.3	NP	NP
% Residual Solvent (Isopropanol)	To be reported	1.7	0.7	0.7	1.7	1.4	1.4
Note Book Reference		192031-46 to 52	192039-9 to 23		192031-46 to 52	192039-9 to 23	

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

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TABLE 33

(65/130 mg/vial, acetonitrile or ethanol as co-solvents)

		Initial NPH22035 Formulation in Acetonitrile:Water		Initial NPH22834 Formulation in Ethanol:Water	
Test	Spec.	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)
Description	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	NA	NA	NA	NA
% Assay Phenobarbital Sodium	90.0%-105.0%	103.6	101.2	100.2	98.3

TABLE 33-continued

(65/130 mg/vial, acetonitrile or ethanol as co-solvents)

		Initial NPH22035 Formulation in Acetonitrile:Water		Initial NPH22834 Formulation in Ethanol:Water	
Test	Spec.	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	ND	ND	ND	ND
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.4	0.4	0.2	0.2
Residual Solvent	To be reported	NA	NA	3.2	19.2

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

Id. at Tables 31-33. The ’076 Patent notes that “although no known degradation products were observed above quantitation limit, the residual solvents [such as isopropanol, tertiary butanol, and ethanol] could not be removed completely after lyophilization.” *Id.* at 57:60-66. The ’076 Patent further states because “organic solvents are toxic to all age groups, and in particular to neonates and because residual solvents are typically trapped in the crystal lattice of the

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Phenobarbital, the lyophilized product with only water as solvent is preferred over formulations containing any organic co solvents." *Id.* at 57:67-58:33.

4. Priority Date of the '076 Patent

On the face of the '076 Patent, the '804 application is a continuation application of the '914 application, filed on June 30, 2022, which is a continuation-in-part of the '881 application[6], filed on September 18, 2020, which claims the benefit of U.S. Provisional Patent Application No. 62/903,511 ("the '511 application"), filed on September 20, 2019.

The '076 Patent includes new subject matter, included in all claims, beyond the disclosure of the '881 application and the '511 application and therefore is not entitled to the priority date of these applications. Specifically, the '076 Patent encompasses broader and different subject matter, including, *inter alia*, ***crystalline*** forms of lyophilized phenobarbital sodium compositions, which were not disclosed in the '881 application and the '511 application. As such, the new and expanded claims in the '076 Patent are not supported by the earlier filed '881 and '511 applications.

The '076 Patent presents extended stability studies of lyophilized amorphous phenobarbital sodium, providing stability data for up to and beyond three years, in contrast to the stability data disclosed in the '881 application and the '511 application. *Compare* Specification at [0082]-[0083] (Tables 2-3), Appl. No. 62/903,511, dated Sept. 20, 2019, *and* Specification at [00105]-[00106], [00130]-[00133], [00139] (Tables 2-3, 10-13, 16), Appl. No. 17/025,881, dated Sept. 17, 2020, *with* '076 Patent at Tables 18-23. As the Examiner for the '881 application noted, the claim limitation of "at least 24 months at room temperature" has "no support from any data"

[6] As discussed above, the '881 application eventually issued as the '598 Patent. *See supra* Section III.A.

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within the specification of the ’881 application. Examiner-Initiated Interview Summary for Appl. No. 17/025,881 dated Mar. 30, 2022. Additionally, the ’076 Patent includes a dependent claim (claim 6) that specifies a limitation of stability at room temperature for 24 months: “The pharmaceutical product of claim 1, 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).” ’076 Patent at cl. 6.

Furthermore, unlike the disclosure of the ’881 application and the ’511 application, which focus solely on ***amorphous*** lyophilized phenobarbital sodium composition, the inventors of the ’076 Patent investigated whether stable lyophilized phenobarbital preparations could be prepared in ***crystalline*** form. *Compare* Specification at [0009], Appl. No. 62/903,511, dated Sept. 20, 2019 (“The contemplated composition is an ***amorphous*** lyophilized Phenobarbital Sodium with high stability and purity.”) (emphasis added), *and* Specification at [0010], Appl. No. 17/025,881, dated Sept. 17, 2020 (same), *with* ’076 Patent at 51:30-34. The Examiner of the ’881 application noted that “crystalline form [of phenobarbital sodium] is ***not*** the claimed subject matter [of the ’881 application and the ’598 Patent].” Office Action for Appl. No. 17/025,881 dated June 1, 2021 at 10 (emphasis added). Because claims 1-4, 6-11, 13-14, and 16-19 of the ’076 Patent are not limited to amorphous forms, they encompass lyophilized phenobarbital sodium compositions in ***both amorphous*** and ***crystalline*** forms. *See* ’076 Patent at cls. 1-4, 6-11, 13-14, 16-19.

Finally, unlike the disclosure of the ’881 application and the ’511 application, which do not include and, in fact, ***exclude*** organic solvents from the phenobarbital sodium solution, the inventors of the ’076 Patent investigated whether stable lyophilized phenobarbital preparations

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could be prepared using one or more water miscible co-solvents, including organic solvents. *Compare* Specification at [0078], Appl. No. 62/903,511, dated Sept. 20, 2019 ("The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates."), *and* Specification at [00101], Appl. No. 17/025,881, dated Sept. 17, 2020 (same), *with* '076 Patent at 51:30-52:35, *and id.* at Tables 31-33. Because claims 1-20 of the '076 Patent do not exclude any organic solvents (absent a finding of disclaimer) within the phenobarbital sodium solution (unlike the '881 application and the '511 application, which were required to do so), claims 1-20 of the '076 Patent encompass phenobarbital sodium compositions ***with and without*** organic solvents. *See* '076 Patent at cls. 1-20.

Therefore, the earliest priority date of the '076 Patent is the priority date of the '914 application, filed on **June 30, 2022**, which discloses the new claim scope: (1) stability of at least 24 months at room temperature, (2) crystalline form of lyophilized phenobarbital sodium composition, and (3) phenobarbital sodium solution with organic solvents. *See* Specification at [0129]-[0135], [0141]-[0156], [0168]-[0180], Tables 10-13, 16, 18-23, 29A-33, Appl. No. 17/854,914, dated June 30, 2022.

IV. LEGAL STANDARDS

A. Claim Construction

Claims are always in the form of a single sentence, usually having a preamble and one or more "elements" or "limitations." The limitations of the claims provide the measure for patentability, as well as infringement. To analyze either the validity or infringement of a patent, therefore, the patent claims must first be construed to determine their proper scope and content. *E.g., Nazomi Communications, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1367-68 (Fed. Cir. 2005) (citing *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. I 998) (*en banc*)).

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Claim construction, including terms of art, is exclusively within the province of a court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996).

Words of a claim are generally given their ordinary and customary meaning. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996)). The ordinary and customary meaning of a claim term is the meaning that the term would have "to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* This meaning was stated by the *Phillips* court to "provide an objective baseline from which to begin claim interpretation." *Id.* Even so, this person of ordinary skill in the art is deemed to have read the claim term not only in the context of the particular claim in which the disputed term appears but also in the context of the entire patent, including the specification and prosecution history of the patent. *Id.* at 1313-14. Proper construction of a patent claim thus requires consideration of all the sources of meaning of the claim in the PTO record, namely the claim language itself, the written description, and the prosecution history, including the prior art cited during the examination of the patent. *Id.* at 1317.

Where the ordinary meaning of a claim term is clear even to the layperson, claim construction "involves little more than the application of the widely accepted meaning of commonly understood words . . . in such circumstances, general purpose dictionaries may be helpful." *Id.* at 1314. Where terms have a particular meaning to those of skill in the art, a court may look to "extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* (internal quotes omitted). Nonetheless, "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id.* at 1315 (citing

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Vitronics, 90 F.3d at 1582). "In light of the statutory directive that the inventor provides a 'full' and 'exact' description of the claimed invention, the specification necessarily informs the proper construction of the claims." *Id.* at 1316.

B. Anticipation (35 U.S.C. § 102)

The Federal Circuit has held that a reference may anticipate inherently if a claim limitation that is not expressly disclosed is "necessarily present, or inherent, in the single anticipating reference." *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012) (quoting *Schering Corp. v. Geneva Pharms., Inc.*, 339. F. 3d 1373, 1377 (Fed. Cir. 2003)). An inherent disclosure is therefore one where the prior art reference discloses subject matter that necessarily includes or satisfies the unstated limitation. *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991 (Fed. Cir. 2006). The Court has explained that the "inherent result must inevitably result from the disclosed steps" and that inherency "may not be established by probabilities or possibilities." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). As such, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

C. Obviousness (35 U.S.C. § 103)

A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 35 U.S.C. § 103. The objective standard for determining obviousness under 35 U.S.C. § 103, as set forth in *Graham v. John Deere, Co.*, 383 U.S. 1 (1966), requires a factual determination to ascertain: (1) the scope and content of the prior art; (2)

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the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art.

Based on these factual inquiries, it must then be determined, as a matter of law, whether or not the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the alleged invention was made. *Id.* at 17.

For a claimed invention to be found obvious, it must have been obvious to a person of ordinary skill in the art at the time the invention was made. *In re Mayne*, 104 F.3d 1339, 1341 (Fed. Cir. 1997). The person of ordinary skill is "a hypothetical person who is presumed to be aware of all the pertinent prior art." *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). The person of ordinary skill is also presumed to possess the common sense and creativity of a real person. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

A claim may be proven obvious in view of a single prior art reference or in view of a combination of prior art references. Although the Supreme Court indicated that a rigid application of the teaching, suggestion, or motivation ("TSM") test is "incompatible with our precedents," *KSR*, 550 U.S. at 418, later Federal Circuit decisions indicate that the TSM test, when applied with flexibility, may be used to conduct an obviousness analysis when references are combined to invalidate a claim under 35 U.S.C. § 103. *See Ortho-McNeil Pharma, Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). That teaching, suggestion, or motivation need not be expressly stated in one or all of the references used to show obviousness, but rather "may be found in any number of sources, including common knowledge, the prior art as whole, or the nature of the problem itself." *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006); *see also Cable Elec. Prods. Inc. v. Genmark, Inc.*, 770 F.2d 1015,

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1025 (Fed. Cir. 1985); *In re Beattie*, 974 F.2d 1309, 1311–12 (Fed. Cir. 1992). Moreover, "the [TSM] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

In rejecting the rigid application of the TSM test, the Supreme Court made it clear that there were many reasons to find a patent obvious based on the prior art. "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." *Id.* at 419; *see also In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992). "The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." KSR, 550 U.S. at 420. Thus, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results," and, under some circumstances, obviousness under § 103 may be proved merely by showing that a combination of elements was "obvious to try." *Id.*

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at 420.

The Federal Circuit has held that the motivation to combine can be found in the knowledge generally available to one of ordinary skill as demonstrated by references that do not qualify as prior art under 35 U.S.C. § 102. *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-1338 (Fed. Cir. 2004). Such references are relevant because they can

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demonstrate the knowledge of one of ordinary skill in the art, even if they are not public information. *Id.* ("We are concerned only with whether the Lund drawing demonstrates that others in Mr. Lund's position (or a more experienced position) would have considered it obvious to combine the [prior art] elements.").

The Federal Circuit has stated that, pursuant to *KSR*, "obvious to try" may be equated with obviousness under § 103 as long as two "pitfalls" are avoided. First, the prior art must give some "indication of which parameters were critical" or "which of many possible choices is likely to be successful" so that the inventor did not have to pursue a dartboard strategy of "vary[ing] all parameters or try[ing] each of numerous possible choices." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Courts have taken a case-by-case approach to determine the degree of narrowing that must be suggested by the prior art to establish obviousness. Second, where determining whether "a new technology or general approach that seem[s] to be a promising field of experimentation" is "obvious to try," the prior art must do more than give "only general guidance as to the particular form of the claimed invention or how to achieve it." *In re Kubin*, 561 F.3d at 1359 (quoting *In re O'Farrell*, 853 F.2d at 903); *see, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (finding more than general guidance where prior art included a list of 53 FDA-approved anions that inventors used to find a pharmaceutically-acceptable salt).

If it is known that some desirable property of a mixture derives in whole or in part from one component of the mixture, the purified compound is "prima facie obvious over prior art references that disclose a mixture even without explicit teachings that the ingredients should be concentrated or purified." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007). Therefore, where one component of a mixture alone provides a

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therapeutic effect, there is "no need to find an express teaching to prove sufficient motivation to modify the prior art" to purify the compound. *Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F.3d 1326 (Fed. Cir. 2015).

In addition, secondary considerations, where present, must be considered by the court. *See Stratoflex, Inc. v. Aeroquip Cor.*, 713 F.2d 1530, 1538 (Fed. Cir. 1998). Secondary considerations that should be considered by the Court include: commercial success of the invention, whether the invention addressed a long-felt need, unexpected results, copying of the invention by others in the field, and failure of others to solve the problem that faced the inventor. *Id.* A nexus must be established between the merits of the claimed invention and any evidence of secondary considerations. *Cable Elec. Prods.*, 770 F.2d at 1027. The stronger the case of obviousness, the more difficult it is for the patentee to rebut the obviousness with secondary considerations; indeed, at some point, no matter what the alleged secondary considerations, a *prima facie* case of obviousness may be so strong that secondary considerations cannot overcome obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) ("[S]econdary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness.").

D. Indefiniteness (35 U.S.C. § 112)

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 898-99 (2014). "[A] patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." *Id.* at 2129 (quotations and citations omitted). The analysis to determine if a claim is invalid for indefiniteness examines the claims, specification, and prosecution history "to ascertain if they convey to one of skill in the art

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with reasonable certainty the scope of the invention claimed." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015).

E. Lack of Written Description (35 U.S.C. § 112)

To satisfy the written description requirement, "the patent specification must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (internal quotations and citation omitted). This means that "the disclosure must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (internal quotations and citation omitted) (affirming district court's finding that the patent claims were invalid); *see also Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005); *In re Curtis*, 354 F.3d 1347, 1350- 52 (Fed. Cir. 2004) (affirming Board's finding that a prior application "did not provide an adequate written description of the later-claimed genus of friction enhancing coatings"); *Purdue Pharma L.P. v. F.H. Faulding & Co.*, 48 F.Supp.2d 420, 427 (D. Del. 1999); *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009) ("[T]he purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not . . . ."); *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (The written description requirement is satisfied only if the inventor "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate[s] that by disclosure in the specification of the patent."). Under this requirement, the patent's specification must describe what is claimed with sufficient detail such that a person of ordinary skill in the art can conclude that "the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed Cir. 2010) (citation omitted); *see also*

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Carnegie Mellon Univ. v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1122 (Fed. Cir. 2008) ("[T]he applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." (citation omitted)).

"[T]he hallmark of written description is disclosure. Thus, 'possession as shown in the disclosure' is a more complete formulation." *Ariad*, 598 F.3d at 1351. The test for written description involves an objective inquiry into whether the specification describes the invention sufficiently to allow a person of ordinary skill in the art to understand it and know that the inventor actually invented the claimed invention. *Id.* The operative time for this determination is the date of the patent's filing. *Id.* ("The law must be applied to each invention at the time it enters the patent process, for each patented advance has a novel relationship with the state of the art from which it emerges."). The Federal Circuit has stated that, when determining whether a patent specification complies with the written description requirement:

> [T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.

Id. (quoting *Capon*, 418 F.3d at 1359). Finally, "actual 'possession' or reduction to practice outside of the specification is not enough . . . it is the specification itself that must demonstrate possession." *Id.* at 1352. Where the specification fails to disclose claimed features such that a POSA "would not have thought it would work," the claims fail to satisfy the written description requirement. *Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1377, 1381-84 (Fed. Cir. 2019).

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F. Lack of Enablement (35 U.S.C. § 112)

Under 35 U.S.C. § 112, ¶ 1, an inventor is obligated to set forth in the specification "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F. 3d 1361, 1365 (Fed. Cir. 1997)); *see also Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993); 35 U.S.C. § 112, ¶ 1. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations," including the quantity of experimentation necessary and the amount of direction or guidance presented. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Enablement of one mode of practicing the invention will not satisfy the enablement requirement if the invention is broadly claimed. *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007); *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1378-79 (Fed. Cir. 2007).

Where one of ordinary skill in the art "would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the . . . specification," the invention is not sufficiently enabled. *Wyeth & Cordis Corp. v. Abbott Labs*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (internal quotations omitted) (affirming summary judgment of invalidity for nonenablement where evaluating claimed candidate compounds would

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"take technicians weeks to complete" and the "specification offer[ed] no guidance or predictions about particular substitutions that might preserve" the effects of the claimed method of treatment); *see also In re '318 Patent Infringement Litig.*, 583 F.3d at 1327 ("Thus, at the end of the day, the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient.").

Whether a patent complies with the enablement requirement is a question of law and is determined from the perspective of a person of ordinary skill in the art as of the filing date of the specification. *EnzoBiochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999). The Court must make an enablement determination "*retrospectively*, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." *Id.* Although the enablement inquiry is viewed from the perspective of a person of ordinary skill in the art, that person's knowledge is not a "substitute for a basic enabling disclosure." *Genentech*, 108 F.3d at 1366 (recognizing that the specification, not knowledge of a person of ordinary skill in the art, must supply novel aspects of an invention to constitute adequate enablement).

V. PERSON OF ORDINARY SKILL IN THE ART

The subject matter of the '598 and '076 Patents falls within the field of pharmaceutical sciences. A person of ordinary skill in the art ("POSA") at the relevant time would typically have at least a Master's, Pharm.D., or Ph.D. in pharmaceutical sciences or a related field, along with several years of experience in developing, making and/or researching pharmaceutical formulations, including experience with lyophilization, injectables, and identifying degradation products of reconstituted pharmaceutical compositions.

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A POSA would also understand that the process of drug product development generally involves a multidisciplinary approach and would have had access to and would have consulted with a collaborative team of ordinarily skilled artisans having specialized skills in various aspects of drug development to solve any given problem. For example, a POSA would have the ability, if necessary, to consult with drug formulators, chemists, medical doctors, and experts with advanced degrees and/or experience in toxicology, analytical chemistry, process chemistry, formulation science, regulatory affairs, pharmacology, and including preclinical and clinical research. Additionally, a POSA would refer to journals, treatises, books, monographs, patents, and other literature related to the field of pharmaceutical sciences and would be familiar with developments reported therein.

VI. SCOPE AND CONTENT OF THE PRIOR ART

A. Karen M. Alsante et al., *Recent Trends in Product Development and Regulatory Issues on Impurities in Active Pharmaceutical Ingredient (API) and Drug Products. Part 2: Safety Considerations of Impurities in Pharmaceutical Products and Surveying the Impurity Landscape*, 15(1) AAPS PHARMSCITECH. 237 (2013) ("Alsante")

Alsante was published in 2013 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Alsante discusses the importance of "control strategies of chemical and physical changes of active pharmaceutical ingredients (API) and drug products in the drug development process," emphasizing that "[t]hese changes can affect both the safety and efficacy of drugs." Alsante at 237. Alsante discloses that "the ability to rapidly predict and assess the potential for drug product performance changes for impurity formation and the associated safety concerns are important parts of speeding the development of innovative drug therapies without compromising quality." *Id.* Alsante notes that "[t]he degree and level of rigor associated with impurity investigations are often dictated by the phase of development of the project," marketing authorizations requiring in-depth investigations of impurities that arise from various sources,

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such as synthetic processes, degradation, and interactions with excipients. *Id.* at 239. During later phases of development, extensive studies are conducted to understand the origin and fate of impurities, which helps in determining significant impurities that need routine monitoring. *Id.* Alsante also covered evolving regulatory expectations and impurity formation science, highlighting the ongoing efforts to improve quality programs and control strategies. *Id.* at 242. Furthermore, Alsante points out that hydrolysis and oxidative degradation are two most common pathways of drug degradation. *Id.* at 243.

B. NEAL G. ANDERSON, PRACTICAL PROCESS RESEARCH & DEVELOPMENT (1st ed. 2000) ("Anderson 2000")

Anderson 2000 was published in 2000 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Anderson 2000 emphasizes the role of "postreaction workup and purification/isolation aspects" in process development for synthetic chemistry. Anderson 2000 at xx. Anderson 2000 "provide[s] a comprehensive, step-by-step, hands-on approach to organic process research and development for the preparation of 'small molecules.'" *Id.* at xxi. One of the primary goals of process optimization is to "maximize the amount of product generated under the reaction conditions . . . by driving the reaction to completion, that is, by consuming any starting material that is charged in limiting amounts and by generating product with a minimal amount of by-products." *Id.* at 165. Anderson 2000 teaches that "[t]he presence of impurities can complicate purifications and decrease isolated yields," highlighting the importance of optimizing conditions to reduce impurity formation. *Id.*

Anderson 2000 also discusses the importance of understanding and controlling impurities in the final product to ensure the safety and efficacy of pharmaceutical compounds. *Id.* at 259. "Impurities in a final product must be known and controlled" because inadequate control can compromise the quality of the drug substance and the safety of the drug product. *Id.* at 259.

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Anderson 2000 further suggests that establishing "routine impurity profiles and levels" early in the development process can help avoid the need to rework batches, ultimately saving time and resources. *Id.* at 261-62.

Furthermore, Anderson 2000 advises that the ideal penultimate compound should be identified early in the development process, with parallel development efforts converging on this compound. *Id.* This approach helps to "freeze the final process" early. *Id.* By setting impurity specifications at acceptable levels in intermediates and reagents, the purification burden for the final product can be "greatly reduced or eliminated." *Id.*

Finally, Anderson 2000 highlights that "[o]nce the structure of the impurities is known, the mechanism of formation can generally be elucidated, and conditions to avoid forming these impurities may be designed." *Id.* at 179. Two fundamental strategies to manage impurities are: "to minimize the formation of an impurity, or to minimize the presence of this impurity in the drug substance." *Id.* at 262. It then provides a schematic explaining the approaches to minimize the presence of impurities in a final product:

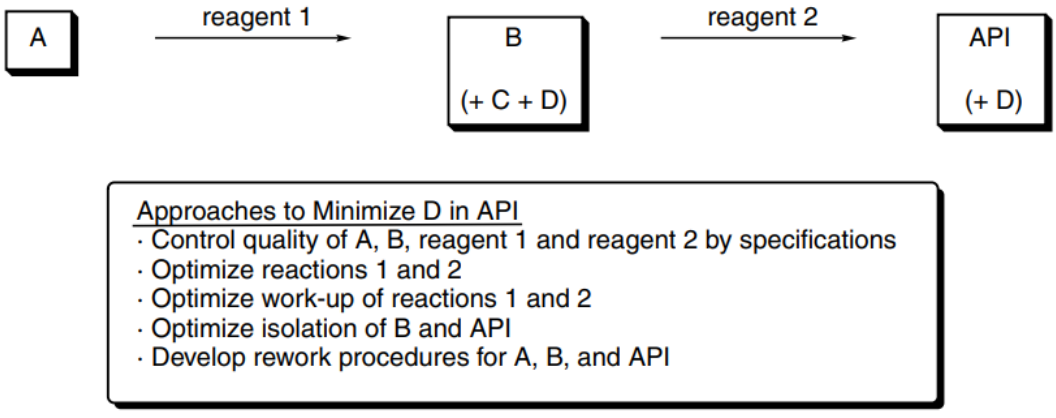


FIGURE 12.6. Approaches to Minimize the Presence of Impurities in a Final Product

Id. at Fig. 12.6.

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C. NEAL G. ANDERSON, PRACTICAL PROCESS RESEARCH & DEVELOPMENT (2d ed. 2012) ("Anderson 2012")

Anderson 2012 was published in 2012 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Anderson 2012 highlights the significant expansion of knowledge in process chemistry over the past decade, noting that "there has been a flood of information on process chemistry, from case studies in articles, to reviews and books, to e-books, blogs and technical information on the internet," and "[w]ith so much information available the foundation of knowledge of process chemists and engineers has expanded and deepened." Anderson 2012 at vii.

Anderson 2012 introduces the ACE strategy—"Avoid, Control, and Expel"—as an effective approach to managing impurities in APIs:

TABLE 13.8 ACE Approach to Minimizing Impurities, Including Genotoxic Impurities

Technique	Examples and Comments
Avoid use or formation	Avoid ICH Class 1 solvents Choose different starting materials Change order of steps in routes
Control formation or decomposition	Mechanistic studies on chemical fate
Expel from product	Chemical fate arguments used in QbD
Extractive workup	Exploit solubility differences
Absorption	Activated carbon, resins
Evaporation	Removing solvents; azeotroping
Selective crystallization	Gradually apply crystallization pressure Exploit solubility differences
Washing product cake	Displace impurities, e.g., high-bp solvents
Drying	Remove VOCs, low-MW compounds

Id. at 384-86, Table 13.8. Anderson 2012 explains that avoiding impurities can involve selecting alternative reagents or routes. *Id.* Anderson 2012 also suggests that expelling impurities from the product can be achieved through methods such as workup and crystallization. *Id.*

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Anderson 2012 describes various strategies to avoid generating hazardous byproducts, including potentially genotoxic impurities (PGIs). Anderson 2012 notes that controlling genotoxic impurities often involves "positioning PGIs early in the route, thus creating more opportunities to purge (expel) them from the APIs." *Id.* One effective strategy includes "(1) positioning a PGI at least four steps from final step, and at each stage analyze potential for processing to remove it; (2) stressing purifications by spiking into process streams additional PGI prior to isolations (process tolerance studies); and (3) monitoring the concentration of the PGI in the penultimate, and setting limit tests." *Id.*

Anderson 2012 underscores the importance of controlling impurities from both economic and moral standpoints, stating that "[t]he economics of failing to control the physical form and impurities in APIs provide good reasons to monitor operations and scrutinize data[, and] from a moral standpoint we must control the impurities in APIs." *Id.* at 389.

D. *Annex 10: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, in* WHO TECHNICAL REPORT SERIES NO. 1010, WORLD HEALTH ORGANIZATION 309-51 (2018) ("Annex 10")

Annex 10 was published in 2018 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Annex 10 highlights that "[i]nformation on the stability of the API is an integral part of the systematic approach to stability evaluation," emphasizing the importance of thoroughly understanding the stability characteristics of active pharmaceutical ingredients and finished pharmaceutical products (FPPs). Annex 10 at 313. Annex 10 suggests that "an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture," ensuring that the selected storage conditions and study durations are adequate to cover both storage and shipment needs. *Id.* at 315. Annex 10 further clarifies that "[s]torage condition tolerances are defined as the acceptable variations in temperature and RH of storage facilities for stability studies." *Id.*

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For FPPs, Annex 10 discloses that the design of the stability studies should be based on "knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies, similar marketed formulations and investigational FPPs." *Id.* at 321.

Annex 10 details the different storage conditions—long-term, accelerated, and intermediate—that should be used:

2.1.7.1 General case

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

Table *continued*

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

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

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

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2.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months or 6 months as referred to in section 2.1.7
Accelerated[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	6 months

[a] Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

2.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	−20 °C ± 5 °C	12 months or 6 months as referred to in section 2.1.7

2.2.7.1 General case

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

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Table *continued*

Study	Storage condition	Minimum time period covered by data at submission
Intermediate[b]	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.

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

See id. at Tables 2.1.7.1-3 (storage conditions for APIs), Table 2.2.7.1 (storage conditions of finished pharmaceutical products).

Annex 10 further highlights that "[s]tability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries," indicating the need for rigorous testing under various environmental conditions to ensure product stability. *Id.* at 324. It notes that "[i]n general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss." *Id.*

E. James C. Bawden et al., *Sterility and Use Patterns of Multiple-Dose Vials*, 39 AM. J. HOSP. PHARM. 294 (1982) ("Bawden")

Bawden was published in 1982 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Bawden investigated the "viability of microorganisms in multiple-dose vials (MDVs) and the use and in-use contamination rate of MDVs." Bawden at 294. Finding that MDVs used for intravenous or intramuscular administration pose a significant infection risk, such as nosocomial infections or bacteremia, Bawden examined their contamination rate. *Id.* In the study, 928 open MDVs were collected from 31 nursing units and pharmacy, concluding that

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although the precise prevalence of contamination could not be determined, the contamination rate appeared to be "below 4 per 1000." *Id.* at 294-96. Due to the "potentially serious consequences to patients should contamination occur," Bawden noted that "many physicians are . . . insisting on opening new vials for each patients and each injections," effectively treating MDVs as single-use vials. *Id.* at 296-97.

F. JOEL BERNSTEIN, POLYMORPHISM IN MOLECULAR CRYSTALS (2002) ("Berstein")

Berstein was published in 2002 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Bernstein teaches that "[a]morphous pharmaceutical materials are typically obtained by employing crystallization procedures far from equilibrium such as (rapid) solidification from the melt, lyophilization (freeze drying) or spray drying, removal of solvent from a solvate, precipitation by changing pH, or by mechanical processing such as granulation, grinding or milling." Bernstein at 254.

G. Odile Bertaux et al., *Modifications of hepatic alpha-1-acid glycoprotein and albumin gene expression in rats treated with phenobarbital*, 203 EUR. J. BIOCHEM. 655 (1992) ("Bertaux")

Bertaux was published in 1992 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Bertaux discloses that "[l]lyophilized sodium phenobarbital (Gardenal for subcutaneous or intramuscular injection, Speck, Paris, France) was dissolved in a pyrogenic sterile normal saline and injected subcutaneously in the interscapulum area daily for 1, 3 or 7 days." Bertaux at 656. Bertaux also describes the dosage administered in the study, stating that "the rats received 75 mg/kg phenobarbital in a volume of 10 ml/kg." *Id.*

H. POLYMORPHISM IN PHARMACEUTICAL SOLIDS (Harry G. Brittain ed., 1999) ("Brittain 1999")

Brittain 1999 was published in 1999 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Brittain 1999 highlights that "[l]yophilization (also known as freeze-drying) is a

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technique that is widely employed for the preparation of dry powders to be reconstituted at the time of administration." Brittain at 213. This technique is particularly advantageous for "compounds that are susceptible to decomposition in the presence of moisture but that are more stable as dry solids," making it a valuable method for preserving the stability of sensitive pharmaceutical compounds. *Id.* at 213-14. Brittain 1999 further explains that "[t]he physical form, chemical stability, and dissolution characteristics of lyophilized products can be influenced by the conditions of the freeze-drying cycle," indicating that careful control of these conditions is important to achieving the desired product qualities. *Id.* at 214.

Brittain 1999 teaches that "lyophilization also can be employed to convert crystalline materials into their amorphous counterparts" and that the lyophilization process typically involves three stages: freezing, primary drying, and secondary drying. *Id.* at 214-15. For the preparation of amorphous materials, "rapid freezing is employed so as to avoid the crystallization process," and "[b]oth aqueous solutions and solutions containing organic solvents have been lyophilized." *Id.* at 215. During the primary drying phase, the process "involves sublimation of frozen water or vaporization of another solvent," achieved by reducing pressure in the chamber and applying heat to the product. *Id.* The secondary drying phase "consists of the desorption of moisture (or residual solvent) from the solid." *Id.*

Brittain 1999 provides "[e]xamples from the literature of excipients and pharmaceuticals prepared as amorphous materials by lyophilization":

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Table 7 Amorphous Pharmaceuticals Obtained by Lyophilization

Compound	Method used	Reference
Lactose	Lyophilization of a 5% Aqueous Solution	[130]
MK-0591	Lyophilization	[131]
Raffinose	Lyophilization of a 10% aqueous solution frozen at −45°C	[132]
Sucrose	Lyophilization of 10% aqueous solutions	[133]
Dirithromycin	Freeze-drying from methylene chloride solution	[134]
Cefalexin	Aqueous solution frozen at −196°C, then freeze-dried	[135]
	Lyophilization of a saturated aqueous solution	[136]
Calcium gluceptate	Freeze-drying from 2% aqueous solution	[137]
Griseofulvin	Freeze-drying of solutions of griseofulvin or of solutions of mixtures of griseofulvin and mannitol in dioxane or 1:1 dioxane-water with fast freezing in liquid nitrogen	[138]
Tolobuterol hydrochloride	Freeze-drying of aqueous solution	[139]
E1040	Freeze-drying of aqueous solution	[140]
Glutathione	Freeze-drying of a 5% aqueous solution	[141]
Aspirin	Freeze drying of an aqueous solution in the presence of 1.0% hydroxypropyl-β-cyclodextrin	[142]
Ketoprofen	Freeze-drying in the presence of heptakis-(2,6-O-dimethyl)-β-cyclodextrin	[143]
	Freeze-drying with β-cyclodextrin (rapid freezing with liquid nitrogen)	[144]
Glibenclamide	Freezing at liquid nitrogen temperature, freeze-drying over 24 hours	[145]

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Table 7 Continued

Compound	Method used	Reference
Naproxen	Colyophilization (223K and 0.013 torr) of naproxen and hydroxyethyl-β-cyclodextrin, or hydroxypropyl-β-cyclodextrin	[146]
Sodium ethacrynate	Rapid freezing of an aqueous solution to −50°C, followed by freeze-drying	[147]
p-Aminosalicylic acid	Colyophilization of *p*-aminosalicylic acid in aqueous solution with pullulan	[148]
Ceftazidime	Freeze-drying a nearly saturated aqueous solution of the free acid	[149]
Cefaclor	Freeze-drying from a nearly saturated aqueous solution	[149]
Cephalothin sodium	Freeze-drying from a 25% aqueous solution	[149]
Cefamandol sodium	Freeze-drying from a 25% aqueous solution	[149]
Cefazolin sodium	Freeze-drying an aqueous solution at low temperature	[149]
Nicotinic acid	Freeze-drying in the presence of β-cyclodextrin (fast-freezing); and heptakis (2,6-O-dimethyl)-β-cyclodextrin	[150]

Id. at 214-16 (Table 7).

I. U.S. Patent No. 8,436,190 ("Brittain '190")

Brittain '190 was issued on May 7, 2013 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Brittain '190 discloses that "[t]he present invention provides pharmaceutical formulations of lyophilized bendamustine suitable for pharmaceutical use" and also outlines "methods of producing lyophilized bendamustine." Brittain '190 at Abstract. Brittain '190 describes that "bendamustine is formulated as a lyophilized powder for injection with 100 mg of drug per 50 mL vial or 25 mg of drug per 20 mL vial," and the vials are

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"reconstituted as close to the time of patient administration as possible" with "Sterile Water for Injection" and "0.9% Sodium Chloride for Injection." *Id.* at 2:3-12.

Brittain '190 further explains the lyophilization process used to produce bendamustine formulations. Initially, the product is "placed in a lyophilization chamber under a range of temperatures and then subjected to temperatures well below the product's freezing point, generally for several hours." *Id.* at 17:63-66. Preferably, the product is kept "at or below about −40° C. for at least 2 hours." *Id.* at 17:66-67. Once freezing is complete, "the chamber and the condenser are evacuated through vacuum pumps, the condenser surface having been previously chilled by circulating refrigerant," "preferably to about −40°, more preferably to about −50° C. or lower, even more preferably to about −60° C. or lower." *Id.* at 17:67-18:6. The evacuation of the chamber continues "until a pressure of about 10 to about 600 microns, preferably about 50 to about 150 microns is obtained." *Id.* at 18:6-9.

Brittain '190 highlights that after freezing, "[t]he product composition is then warmed under vacuum in the chamber and condenser," a process that involves "warming the shelves within the lyophilizer on which the product rests . . . at a pressure ranging from about 10 to about 600 microns." *Id.* at 18:10-14. The warming process is done gradually, "over the course of several hours," with the product temperature initially increased "from about −30° C. to about −101° C. and maintained for about 10-70 hours." *Id.* at 18:14-18. Further, "the product temperature can be increased from the freezing temperature to about 25° C.-40° C. over a period of 30-192 hours." *Id.* at 18:18-21. To prevent issues such as "powder ejection of the lyophilate from vials," the removal of organic solvents and water should be thorough during the initial drying phase, with complete drying confirmed by "stabilization of vacuum, condenser temperature and product shelf temperature." *Id.* at 18:21-25. Finally, after the initial drying, the

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product temperature is "increased to about 25° C.-40° C. and maintained for about 5-40 hours." *Id.* at 18:25-27.

J. Joanne Broadhead, *Parenteral Dosage Forms, in* PHARMACEUTICAL PREFORMULATION AND FORMULATION: A PRACTICAL GUIDE FROM CANDIDATE DRUG SELECTION TO COMMERCIAL DOSAGE FORM 331 (Mark Gibson ed., 2001) ("Broadhead")

Broadhead was published in 2001 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Broadhead discusses the definition and scope of parenteral administration, explaining that while the term technically includes all non-oral routes, "[t]he pharmaceutical convention, however, is to use the term parenteral to describe medicines administered by means of an injection." Broadhead at 331. Broadhead further teaches that "[t]he most common routes of parenteral administration are intravenous (IV), subcutaneous and intramuscular, but there are a variety of lesser used routes, such as intra-arterial," and "products such as subcutaneous implants are usually classed as parenterals." *Id.* Broadhead discloses that parenterals can be added to 5% dextrose or 0.9% sodium chloride infusion/injection for administration. *Id.* at 332.

Broadhead identifies hydrolysis as the "most common mechanism of instability in parenteral formulations," largely due to the presence of water as a major component, whether the formulation is a solution, emulsion, or contains a complexing agent. *Id.* at 340. To address this instability, Broadhead teaches that the removal of water is often important, with lyophilization being the preferred method due to its effectiveness and ability to be conducted in an aseptic environment. *Id.*

Broadhead discloses that lyophilization is "essentially a three-stage process" that begins with freezing the product to low temperatures (typically, –30 to –40°C), followed by primary drying under high vacuum to sublimate the ice, and secondary drying under vacuum to 20–40°C to remove any remaining moisture by desorption. *Id.* This process results in a product with very

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low moisture content (less than 2 percent) and creates an inert environment within the vials by backfilling them with nitrogen before stoppering. *Id.*

K. Ian B. Butler et al., *Removal of Dissolved Oxygen from Water: A Comparison of Four Common Techniques*, 41(2) TALANTA 211 (1994) ("Butler")

Butler was published in 1994 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Butler examines "[f]our common techniques for the removal of dissolved oxygen from water," which include "boiling at 1 atm, boiling under reduced pressure, purging with N, and sonication under reduced pressure." Butler at Abstract. Butler identifies "[n]itrogen purging for 20-40 min at flow rate of 25 mL/s" as "the most effective oxygen removal method," achieving a "concentration of residual dissolved oxygen" at 0.2-0.4 ppm. *Id.* This technique is particularly significant in experiments involving "redox sensitive reagents," where the removal of dissolved oxygen is important. *Id.* at 211.

Butler explains that "[d]issolved oxygen can be removed from solution by both chemical and physical means," which chemical methods often proving to be "extremely effective." *Id.* For the nitrogen purging method, "[a] glass bubbler was fitted and the water was bubbled with prepurified grade nitrogen for 5, 20, 40 and 60 min at room temperature." *Id.* Butler reports the concentration levels of oxygen in deionized water after various treatments to remove dissolved oxygen, confirming the effectiveness of nitrogen purging in reducing oxygen concentration to minimal levels:

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Table 2. Oxygen concentrations of deionized water after treatment to remove dissolved oxygen[1]

Method	Time	Concentration O_2
N_2 purging	5 mins	0.47 ppm ± 0.05 ppm
(pre-purified grade,	5 mins	0.56 ppm ± 0.05 ppm
<5 ppm O_2)	5 mins	0.55 ppm ± 0.05 ppm
	20 mins	0.35 ppm ± 0.05 ppm
	20 mins	0.33 ppm ± 0.05 ppm
	20 mins	0.42 ppm ± 0.05 ppm
	20 mins	0.34 ppm ± 0.05 ppm
	20 mins	0.36 ppm ± 0.05 ppm
	40 mins	0.18 ppm ± 0.05 ppm
	40 mins	0.23 ppm ± 0.05 ppm
	60 mins	0.19 ppm ± 0.05 ppm
	60 mins	0.22 ppm ± 0.05 ppm
(Ultra high purity	30 mins	0.28 ppm ± 0.05 ppm
grade, <0.5 ppm O_2)	30 mins	0.24 ppm ± 0.05 ppm
	30 mins	0.30 ppm ± 0.05 ppm
	30 mins	0.28 ppm ± 0.05 ppm
Boiling at 1 atm	30 mins	1.20 ppm ± 0.05 ppm
	30 mins	1.21 ppm ± 0.05 ppm
	30 mins	0.87 ppm ± 0.05 ppm
	30 mins	0.93 ppm ± 0.05 ppm
	30 mins	0.77 ppm ± 0.05 ppm
	30 mins	0.75 ppm ± 0.05 ppm
	30 mins	1.00 ppm ± 0.05 ppm
	30 mins	0.85 ppm ± 0.05 ppm
Boiling under	30 mins	0.34 ppm ± 0.05 ppm
reduced pressure	30 mins	0.31 ppm ± 0.05 ppm
	30 mins	0.31 ppm ± 0.05 ppm
	30 mins	0.28 ppm ± 0.05 ppm
	30 mins	0.28 ppm ± 0.05 ppm
	30 mins	0.26 ppm ± 0.05 ppm
Sonication under	30 mins	6.92 ppm ± 0.05 ppm
reduced pressure	60 mins	0.67 ppm ± 0.05 ppm
	30 mins	2.38 ppm ± 0.05 ppm
	30 mins	1.18 ppm ± 0.05 ppm
	60 mins	0.55 ppm ± 0.05 ppm
	60 mins	0.49 ppm ± 0.05 ppm

[1]Concentrations derived from analysis of iodine produced directly from oxidation of manganese hydroxides by oxygen. Errors are the random errors due to uncertainty in experimental technique.

Id. at Table 2.

Butler highlights that "[p]urging with nitrogen appears to be both a quick and effective procedure to scrub deionized water of dissolved oxygen." *Id.* at 213. Butler recommends using "pre-purified grade nitrogen, a sintered glass bubbler, high gas flow rates and an air-tight container (with a small vent hole to let the purge gas out) for effective removal of oxygen by this method." *Id.* at 214. Additionally, Butler points out that "[n]itrogen purging does also have the

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virtue that the solution is cool and ready for use immediately after oxygen removal," making it a convenient choice compared to other methods. *Id.* However, a potential drawback noted is that "there will be nitrogen in solution after oxygen removal." *Id.*

L. Duncan Q.M. Craig et al., *The relevance of the amorphous state to pharmaceutical dosage forms: glassy drugs and freeze dried systems*, 179(2) INT. J. PHARM. 179 (1999) ("Craig")

Craig was published in 1999 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Craig highlights that "[m]any pharmaceuticals, either by accident or design, may exist in a total or partially amorphous state." Craig at Abstract. The physical structures of solid drugs and dosage forms are "relatively simple to study using techniques such as differential scanning calorimetry and X-ray diffraction." *Id.* at 179. Craig teaches that processes such as "freeze and spray drying may lead to the generation of amorphous systems." *Id.* at 180. Additionally, Craig suggests that "the drug, excipient or delivery system may be deliberately produced in an amorphous form in order to enhance product performance characteristics." *Id.* at 180.

Craig further elaborates that "[f]reeze-drying has been used as a pharmaceutical unit operation for a number of years," particularly for pharmaceuticals of biological origin. *Id.* at 198. Freeze drying involves "the desiccation of a substance by crystallisation of ice, followed by sublimation of water vapour from the solid state at reduced pressure." *Id.* at 198.

Craig describes the stages of the freeze-drying process in detail. The initial freezing phase occurs when aqueous solutions are cooled "to temperatures below 0°C," leading to ice nucleation and subsequent crystal growth as molecular mobility decreases. *Id.* at 199. During primary drying, the ice formed during the freezing stage "is removed by sublimation under vacuum," effectively separating the water from the solute phase. *Id.* at 200. The secondary drying phase focuses on removing "unfrozen" water from the freeze concentrate, which is facilitated by

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"increasing the shelf temperature, usually to 25–60°C." *Id.* at 201. Craig emphasizes that "it is very important that all ice has been removed by sublimation before the temperature is raised in order to prevent melt-back," particularly in the case of amorphous products, where the remaining water after primary drying is "trapped in the glassy phase." *Id.*

M. *Deliberation Results Report: Nobelbar for intravenous injection 250 mg*, JAPAN EVALUATION AND LICENSING DIVISION, PHARMACEUTICAL AND FOOD SAFETY BUREAU (Sept. 16, 2008) ("Deliberation Results Report")

The Deliberation Results Report was published in 2008 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. The Deliberation Results Report discloses the review outcomes by the Pharmaceuticals and Medical Devices Agency for "Nobelbar for intravenous injection 250 mg," a lyophilized drug product containing "274 mg of phenobarbital sodium (250 mg as phenobarbital) per vial." Deliberation Results Report at 1.

The report indicates that "the efficacy and safety of this drug for neonatal convulsion and status epilepticus have been demonstrated." *Id.* at 2. Following the review, the approved indications and dosages were specified for "neonatal convulsion" and "status epilepticus," with an initial intravenous dose of 20 mg/kg as phenobarbital for neonatal convulsions and maintenance doses between 2.5 - 5 mg/kg." *Id.* For status epilepticus, the recommended intravenous dosage is 15 - 20 mg/kg of phenobarbital once daily." *Id.*

The Deliberation Results Report provides a historical perspective on phenobarbital, stating that it was developed by Bayer AG in 1912 and is widely used globally for its "anticonvulsant, hypnotic, and sedative effects." *Id.* at 3. It is available in various formulations, including oral, injectable, and suppository forms, and is approved in multiple countries for different routes of administration. *Id.* In Japan, phenobarbital sodium has been approved for subcutaneous and intramuscular use since 1949, with additional formulations such as suppositories approved later. *Id.*

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The report also discusses the drug substance's properties, describing phenobarbital sodium as "a white crystal or crystalline powder" that is "hygroscopic" and can change forms at a relative humidity of 68% or higher. *Id.* at 4. Despite these properties, "the difference in the crystalline form of the drug substance is judged to have no effect on the manufacture of the drug substance," as the drug product is a lyophilized formulation prepared by dissolving the drug substance in water. *Id.* The report also notes the solubility challenges, stating that "phenobarbital is extremely slightly soluble in water." *Id.* at 5. The stability of the drug substance was rigorously evaluated through various storage tests, including long-term, accelerated, and intermediate tests, which showed "no clear changes" in any of the measurements, leading to a storage recommendation of "tight container, room temperature storage" with a re-test period of five years. *Id.*

Furthermore, the Deliberation Results Report highlights that the drug product is a "lyophilized injection composed of drug substance only, without additives," and stored in "a clear colorless glass vial/rubber stopper/flip cap" system. *Id.* The stability of the drug product was assessed through extensive tests, including long-term storage, accelerated, and caustic tests, all of which indicated "no clear changes" in any test items, thereby confirming the product's stability over its shelf life. *Id.* The Deliberation Results Report also reports that the drug product is "stored at room temperature" with a set expiry date of three years. *Id.*

N. *Guideline on the Limits of Genotoxic Impurities, Committee for Medicinal Products or Human Use,* EMEA/CHMP/QWP/251344/2006, EUROPEAN MEDICINES AGENCY (June 2006) ("EMEA Guideline")

The EMEA Guideline was published in 2006 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. The EMEA Guideline discusses the complexities surrounding "[t]the toxicological assessment of genotoxic impurities and the determination of acceptable limits for such impurities in active substances," noting that this issue is "not addressed in sufficient detail

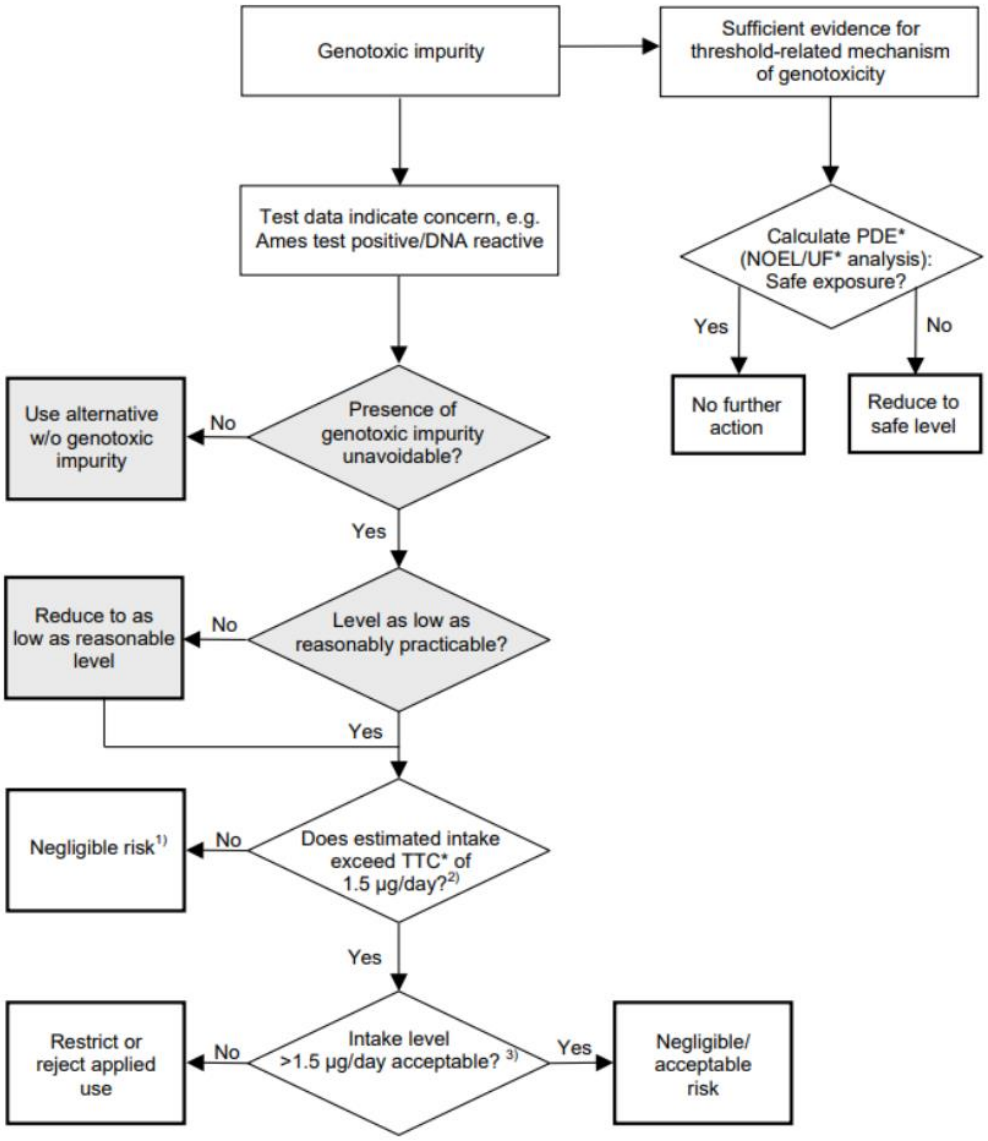
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in the existing ICH Q3X guidances." EMEA Guideline at 3. The EMEA Guideline emphasizes that "actual and potential impurities most likely to arise during synthesis, purification and storage of the new drug substance should be identified," which requires a "sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials," and any "possible degradation products." *Id.* at 4.

The EMEA Guideline further instructs that "potential genotoxic impurities should be identified" based on "existing genotoxicity data or the presence of structural alerts." When an impurity shows structural alerts indicating potential genotoxicity, "additional genotoxicity testing of the impurity, typically in a bacterial reverse mutation assay, should be considered." *Id.*

For impurities where "no threshold mechanisms are identified," the EMEA Guideline states that the "assessment of acceptability of genotoxic impurities . . . should include both pharmaceutical and toxicological evaluations." *Id.* at 5. It suggests following the ALARP principle ("as low as reasonably practicable") to control impurity levels where complete avoidance is not feasible:

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Id. at 5, 7. The EMEA Guideline also notes that "levels considered being consistent with the ALARP principle following pharmaceutical assessment should be assessed for acceptability from a toxicological point of view." *Id.* at 5.

Moreover, the EMEA Guideline highlights that "[i]f a genotoxic impurity is considered to be unavoidable in a drug substance," there should be "technical efforts (e.g. purification steps)" to reduce the impurity content in the final product to ensure safety or "to a level as low as reasonably practicable." *Id.*

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O. *ICH Topic Q1A Stability Testing Guidelines: Stability Testing of New Drug Substances and Products - Step 5*, CPMP/ICH/380/95, EMEA (1995) ("EMEA ICH Topic Q1A")

EMEA ICH Topic Q1A was published in 1995 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. EMEA ICH Topic Q1A outlines the stability testing requirements for Registration Applications across the European Community (EC), Japan, and the USA, providing a "core stability data package required for new drug substances and products" while allowing for scientifically justifiable alternative approaches. EMEA ICH Topic Q1A at 1. It discloses that stability testing aims to provide evidence of how the quality of a drug substance or product changes over time under various environmental conditions, such as temperature, humidity, and light, to establish "recommended storage conditions, re-test periods and shelf lives." *Id.* Stress testing is important as it helps determine the "intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used." *Id.* at 2. "The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use," with temperature-sensitive substances requiring specific storage and testing conditions. *Id.* at 3. EMEA ICH Topic Q1A teaches that the design of stability studies must be robust, testing a minimum of three batches to establish a retest period or shelf life, with a focus on understanding degradation mechanisms and employing statistical methods to ensure confidence in the results. *Id.* at 4, 7-8. EMEA ICH Topic Q1A also emphasizes "the importance of addressing stability post-reconstitution or dilution to ensure comprehensive data support for labeling and storage instructions." *Id.* at 6-8. EMEA ICH Topic Q1A specifies that long-term stability testing should be conducted at conditions of 25°C ± 2°C and 60% RH ± 5% for at least 12 months, while accelerated stability testing is performed at 40°C ± 2°C and 75% RH ± 5% for at least 6 months. *Id.* at 3, 6.

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P. Tomaž Einfalt et al., *Methods of amorphization and investigation of the amorphous state*, 63 ACTA PHARM. 305 (2013) ("Einfalt")

Einfalt was published in 2013 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Einfalt notes that amorphous solids are characterized by "a crystal-like short-range molecular arrangement, but lacking a long-range order." Einfalt at 305. Einfalt highlights various methods of solid-state amorphization, including supercooling of liquids, milling, lyophilization, spray drying, and dehydration of crystalline hydrates. *Id.* at Abstract. Einfalt discloses that the amorphous form of pharmacologically active materials is of significant interest because it represents "it represents the most energetic solid state of a material, and should thus provide the biggest advantages in terms of dissolution rate and bioavailability." *Id.* at 305. Einfalt further teaches that due to their "higher Gibbs free energy than their crystalline counter parts," amorphous materials exhibit "higher apparent solubility and faster dissolution rates, which in turn can lead to higher bioavailability for drugs that exhibit dissolution-rate limited absorption." *Id.* at 307. However, "due to excess entropy, enthalpy and free energy that account for better solubility, the amorphous state is inherently unstable and recrystallization may occur." *Id.* Einfalt further discloses that amorphous materials are typically prepared through methods like "quench cooling of the melt or rapid precipitation from solution," with lyophilization being a common technique for producing amorphous or partially amorphous systems in pharmaceutical applications. *Id.* at 308-09.

Q. *Lyophilization of Parenteral (7/93): Guide to Inspection of Lyophilization of Parenterals*, U.S. FOOD AND DRUG ADMINISTRATION (1993), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/lyophilization-parenteral-793 ("FDA_7/93")

FDA_7/93 was published in 1993 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. FDA_7/93 describes lyophilization or freeze drying as a process where "water is removed from a product after it is frozen and placed under a vacuum," enabling ice to transition

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"directly from solid to vapor without passing through a liquid phase." FDA_7/93. The process comprises "three separate, unique, and interdependent processes; freezing, primary drying (sublimation), and secondary drying (desorption)." *Id.*

FDA_7/93 outlines the steps generally involved in the lyophilization process, including "dissolving the drug and excipients in a suitable solvent," "sterilizing the bulk solution by passing it through a 0.22 micron bacteria-retentive filter," "filling into individual sterile containers and partially stoppering the containers under aseptic conditions," and "transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions." *Id.* The subsequent steps involve "freezing the solution" and "applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state." *Id.* The process is completed by "complete stoppering of the vials," which is usually performed by "hydraulic or screw rod stoppering mechanisms installed in the lyophilizers." *Id.*

FDA_7/93 highlights several advantages of lyophilization, such as the "ease of processing a liquid, which simplifies aseptic handling," "enhanced stability of a dry powder," "removal of water without excessive heating of the product," and "rapid and easy dissolution of reconstituted product." *Id.* However, there are also disadvantages, including "increased handling and processing time," the "need for sterile diluent upon reconstitution," and the "cost and complexity of equipment." *Id.*

FDA_7/93 notes that "products are manufactured in the lyophilized form due to their instability when in solution," emphasizing that "bioburden should be minimal" and must be determined "prior to sterilization of these bulk solutions prior to filling." *Id.* After the sterilization of the lyophilizer and aseptic loading, the initial step is "freezing the solution," typically "at a temperature well below the eutectic point." *Id.* It is important "during primary

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drying to hold the drying temperature (in the product) at least 4-5°C below the eutectic point" to ensure product quality, and manufacturers should have the necessary "instrumentation to assure the uniformity of product temperatures." *Id.*

FDA_7/93 also discusses concerns regarding the "amount of moisture present in vials," advising that "the manufacturer's data for the establishment of moisture specifications for both product release and stability should be reviewed." *Id.* This includes ensuring that "the expiration date and moisture limit" are established based on worst-case data to demonstrate "adequate stability at the moisture specification." *Id.* Additionally, stability testing should "include provisions for the assay of aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labeling." *Id.*

R. *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products*, U.S. FDA (Nov. 2003) ("FDA Guidance for Industry Q1A(R2)")

Guidance for Industry Q1A(R2) was published in 2003 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. FDA Guidance for Industry Q1A(R2) "define[s] what stability data package for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan, and the United States." FDA Guidance for Industry Q1A(R2) at 1. FDA Guidance for Industry Q1A(R2) outlines "the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated." *Id.* FDA Guidance for Industry Q1A(R2) explains that the primary purpose of stability testing is "to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to

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establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions." *Id.* at 2.

FDA Guidance for Industry Q1A(R2) emphasizes the importance of stress testing, which helps identify likely degradation products, establish degradation pathways, and validate the stability-indicating power of analytical procedures. *Id.* at 3. As explained by FDA Guidance for Industry Q1A(R2), "[t]he nature of the stress testing will depend on the individual drug substance and the type of drug product involved," and it typically involves evaluating the effects of temperature, humidity, oxidation, and photolysis, among other factors. *Id.* FDA Guidance for Industry Q1A(R2) also details the selection of batches for stability studies, recommending that data be provided on at least three primary batches manufactured using the same process as intended for production. *Id.* at 3, 8. These studies should simulate the final production process and use the same or similar packaging systems as those proposed for storage and distribution. *Id.* at 3-4, 8-9.

FDA Guidance for Industry Q1A(R2) further outlines the testing frequency and storage conditions necessary for stability studies. Long-term studies should typically involve testing every three months during the first year, every six months during the second year, and annually thereafter. *Id.* at 4, 9-10. The storage conditions should test thermal stability and sensitivity to moisture, ensuring the drug substances and drug products are sufficient to cover storage, shipment, and subsequent use:

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a. General case (2.1.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

a. General case (2.2.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Id. at 4-5, 7, 10-11. FDA Guidance for Industry Q1A(R2) further discloses that the stability data should be analyzed using appropriate statistical methods to ensure confidence in the stability predictions, and limited extrapolation of real-time data may be used to extend the shelf life if justified. *Id.* at 7, 15-16.

S. Thierry Fournier et al., *Phenobarbital induction of α_1-acid glycoprotein in primary rat hepatocyte cultures*, 20(6) HEPATOLOGY 1584 (1994) ("Fournier")

Fournier was published in 1994 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Fournier discloses the use of "[l]yophilized sodium phenobarbital (Gardenal for subcutaneous or intramuscular injection; Specia, Paris, France)" in experimental procedures

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where the substance was "dissolved or diluted in William's E medium and added to primary cultures." Fournier at 1584.

T. John K. Haleblian, *Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications*, 64(8) J. PHARM. SCI. 1269 (1975) ("Haleblian")

Haleblian was published in 1975 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Haleblian reports that amorphous compounds in pharmaceuticals offer distinct advantages, despite their inherent thermodynamic instability. Haleblian at 1273. It also discloses that the preparation of amorphous solids can be achieved through methods such as lyophilization. *Id.* at 1272 (noting lyophilization of fluprednisolone in *tert*-butanol). Haleblian further teaches that while these compounds can be "unstable chemically in a solution" and "tend to revert to a more stable form," particularly "when the formulation is in aqueous suspension," "the amorphous solids [are typically] more soluble than the crystalline" counterparts. *Id.* at 1273. For instance, Haleblian notes that amorphous forms of certain drugs, like novobiocin acid, have been found to be "at least 10 times more soluble than the crystalline acid." *Id.* Additionally, Haleblian finds that the absorption of amorphous forms can be "definitely superior," as demonstrated in the case of chloramphenicol palmitate in children." *Id.* at 1274.

U. *2018 Injectable Product Catalog*, HIKMA (2018) ("Hikma")

Hikma was published in 2018 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Hikma is a 2018 injectable product catalog, disclosing concentrations of "Phenobarbital Sodium Injection, USP C-IV" available at 65 mg/mL and 130 mg/mL with a 1 mL fill volume. Hikma at 35, 62.

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V. *Impurities in New Drug Substances Q3A(R2)*, INTERNATIONAL CONFERENCE ON HARMONISATION (2006) ("ICH Q3A(R2)")

ICH Q3A(R2) was published in 2006 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. ICH Q3A(R2) provides comprehensive "guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state." ICH Q3A(R2) at 1. It categorizes impurities into three main types: "Organic impurities (process- and drug-related)," "Inorganic impurities," and "Residual solvents." *Id.*

ICH Q3A(R2) highlights that applicants "should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance." *Id.* at 2. This summary should be "based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products." *Id.* Additionally, the studies conducted should "characterise the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold":

ATTACHMENT 1
Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[1] The amount of drug substance administered per day

[2] Higher reporting thresholds should be scientifically justified

[3] Lower thresholds can be appropriate if the impurity is unusually toxic

Id. at 2, Attachment 1.

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ICH Q3A(R2) explains that the "[i]dentification of impurities present at an apparent level of not more than (=) the identification threshold is generally not considered necessary." *Id.* at 2. However, "analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (=) the identification threshold." *Id.* It further states that "all impurities should be qualified." *Id.*

According to ICH Q3A(R2), "[a] rationale for the inclusion or exclusion of impurities in the specification should be presented," including a "discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process." *Id.* at 4. This rationale should include specified identified impurities along with specified unidentified impurities estimated to be present at a level greater than the identification threshold. *Id.* For impurities that are "known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled." *Id.*

ICH Q3A(R2) also discusses "qualification," which is defined as "the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified." *Id.* at 5. The applicant is required to "provide a rationale for establishing impurity acceptance criteria that includes safety considerations." *Id.* Impurities that have been "adequately tested in safety and/or clinical studies would be considered qualified," as well as impurities that are "significant metabolites present in animal and/or human studies." *Id.* ICH Q3A(R2) permits a higher level of a qualified impurity than that present in the

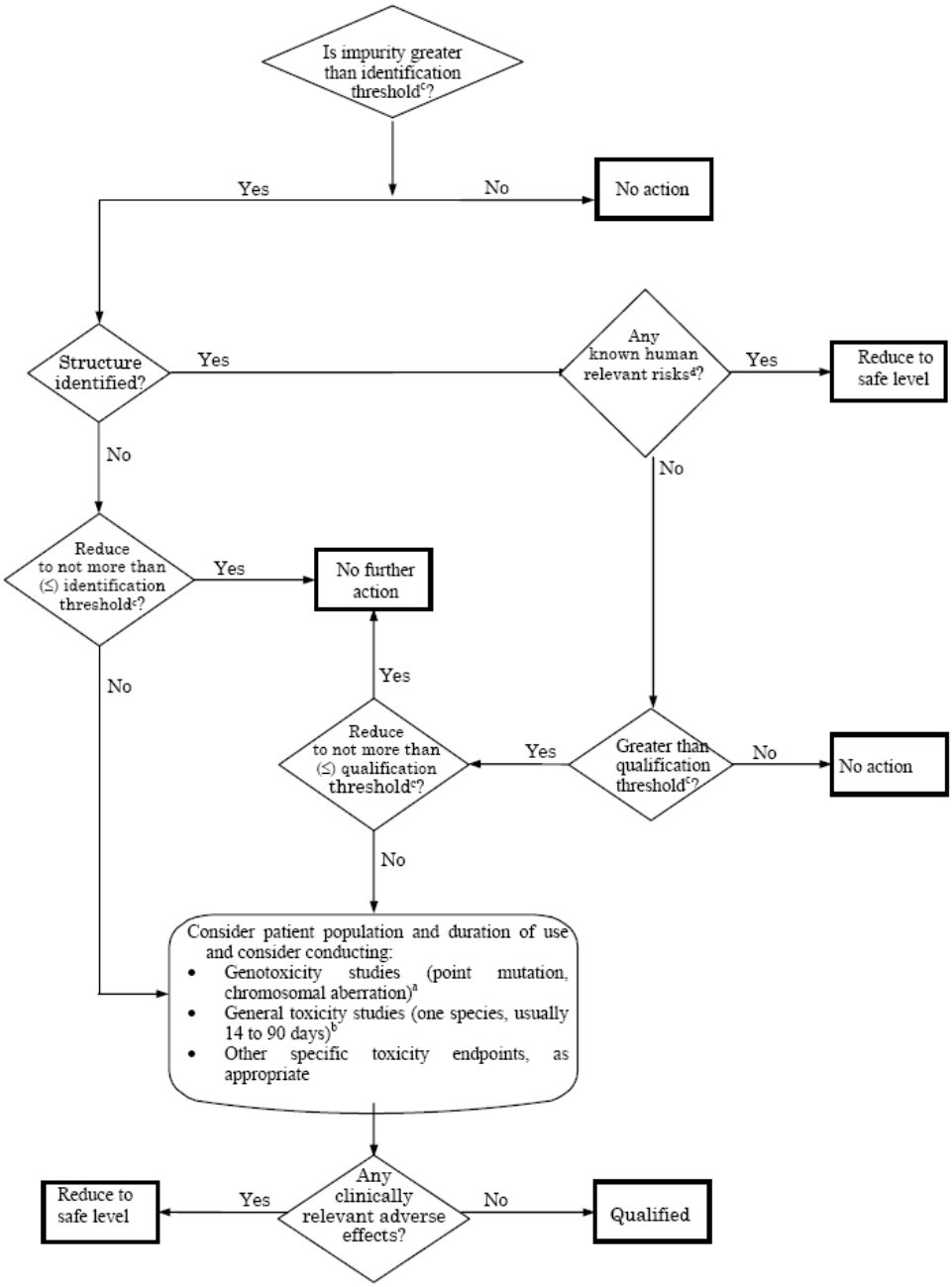
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new drug substance if justified "based on an analysis of the actual amount of impurity administered in previous relevant safety studies." *Id.*

ICH Q3A(R2) includes a "Decision Tree for Identification and Qualification," which outlines "considerations for the qualification of impurities when thresholds are exceeded":

ATTACHMENT 3

Decision Tree for Identification and Qualification



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Id. at 6, Attachment 3. ICH Q3A(R2) also provide guidance for when lower thresholds may be appropriate, particularly "if the impurity is unusually toxic" and emphasizes that known safety data or structural class considerations should inform decisions about human exposure limits. *Id.* at 11.

W. *Impurities in New Drug Products Q3B(R2)*, INTERNATIONAL CONFERENCE ON HARMONISATION (2006) ("ICH Q3B(R2)")

ICH Q3B(R2) was published in 2006 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. ICH Q3B(R2) "provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesised new drug substances not previously registered in a region or member state." ICH Q3B(R2) at 1. ICH Q3B(R2) is complementary to the ICH Q3A(R), which should be referred to for basic principles. *Id.* ICH Q3B(R2) specifically "addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system." *Id.*

ICH Q3B(R2) states that "the applicant should summarise the degradation products observed during manufacture and/or stability studies of the new drug product." *Id.* This summary should be "based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system." *Id.* Additionally, it requires that "the applicant should summarise any laboratory studies conducted to detect degradation products in the new drug product," including "test results of batches manufactured during the development process and batches representative of the proposed commercial process." *Id.* ICH Q3B(R2) also emphasizes that "a rationale should be provided for exclusion of those impurities that are not degradation products," such as "process impurities from the drug substance and impurities arising from excipients." *Id.*

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ICH Q3B(R2) mandates that "any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds":

Attachment 1: Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Notes on Attachment 1

1 The amount of drug substance administered per day

2 Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

3 Higher thresholds should be scientifically justified.

Id. at 1-2, Attachment 1. Furthermore, "analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than the identification threshold." *Id.* at 2.

ICH Q3B(R2) describes "qualification" as "the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified." *Id.* at 4. It specifies that "the applicant should provide a rationale for establishing degradation product acceptance criteria that includes safety

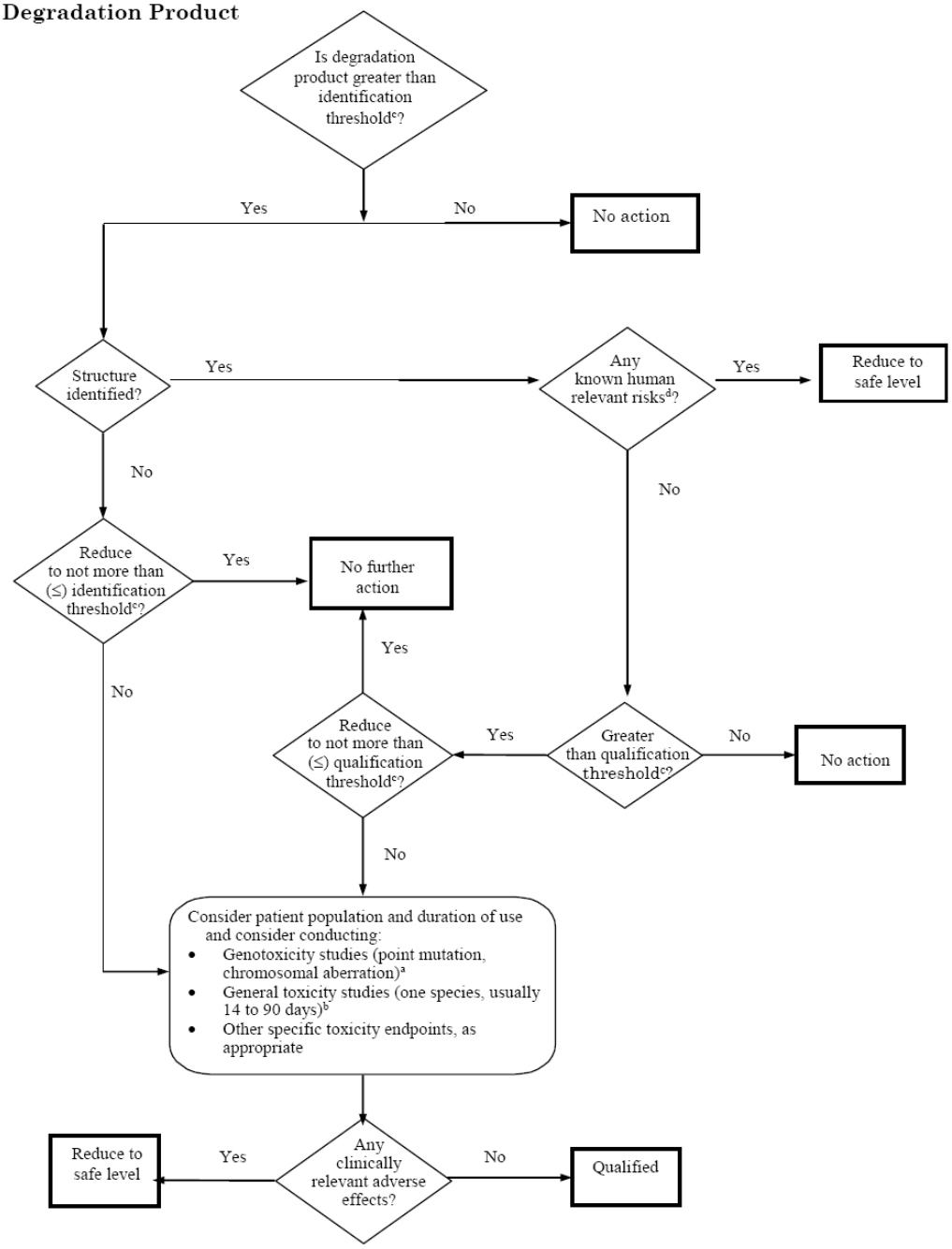
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considerations." *Id.* The level of any degradation product present in a new drug product that has been "adequately tested in safety and/or clinical studies would be considered qualified." *Id.*

ICH Q3B(R2) also discusses justification for higher levels of degradation products, stating that such justification should "include consideration of factors such as: (1) the amount of degradation product administered in previous safety and/or clinical studies and found to be safe; (2) the increase in the amount of the degradation product; and (3) other safety factors, as appropriate." *Id.* at 5. The guideline includes a "Decision Tree for Identification and Qualification of a Degradation Product" that "describes considerations for the qualification of degradation products when thresholds are exceeded":

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Attachment 3: Decision Tree for Identification and Qualification of a Degradation Product



Id. at 5, Attachment 3. Further, ICH Q3B(R2) states that "[i]f considered desirable, a minimum screen (e.g., genotoxic potential), should be conducted," including "[a] study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen." *Id.* at 11. It also advises that "[i]f general toxicity studies are

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desirable, one or more studies should be designed to allow comparison of unqualified to qualified material," with the study duration "based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of a degradation product." *Id.* Additionally, "lower thresholds can be appropriate if the degradation product is unusually toxic." *Id.*

X. THE JAPANESE PHARMACOPOEIA, JAPANESE MINISTRY OF HEALTH, LABOUR AND WELFARE (17th ed. 2016) ("Japanese Pharmacopoeia")

Japanese Pharmacopoeia was published in 2016 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Japanese Pharmacopoeia provides a monograph for phenobarbital, identified by the chemical formula "$C_{12}H_{12}N_2O_3$" and a molecular weight of 232.24. Japanese Pharmacopoeia at 1389. Phenobarbital is also known as "5-Ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione." *Id.* Japanese Pharmacopoeia describes phenobarbital as occurring "as white crystals or crystalline powder." *Id.* It is noted for its solubility properties: "very soluble in *N*,*N*-dimethylformamide, freely soluble in ethanol (95) and in acetone, sparingly soluble in acetonitrile, and very slightly soluble in water." *Id.* The pH of a saturated solution of phenobarbital is reported to be "between 5.0 and 6.0." *Id.*

Y. Kou Kawada, *Phenobarbital sodium lyophilized formulation: Overview of the clinical trial leading to approval of "NOBELBAR®" and package insert information*, 22(7) NEONATAL CARE 657 (2009) ("Kawada 2009")

Kawada 2009 was published in 2009 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Kawada 2009 highlights that the phenobarbital sodium lyophilized formulation "NOBELBAR® 250mg for Injection" "is easily dissolved in water," but "the ingredient changes over time when dissolved." Kawada 2009 at 9. Kawada 2009 points out that this formulation is "relatively unstable," noting that "it is decomposed by about 6% in 24 hours after dissolution." *Id.* Kawada 2009 further emphasizes that "when possible, it is preferable to use a drug product

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that does not contain these additives especially in newborns and low birth weight infants." *Id.* at 12. Kawada 2009 also underscores that there has been "strong[] desire[] by academic societies" in Japan for the "early development of intravenous preparations containing no additives." *Id.* at 13. Additionally, Kawada 2009 provides the description in the package insert of Nobelbar:

Table NOBELBAR® Overview

Brand name:	NOBELBAR® 250mg for intravenous injection
Ingredient and content	274 mg of phenobarbital sodium per vial (250 mg as phenobarbital)
Additive	None
pH	9.2 to 10.2 (when 1g is dissolved in 10mL of water)
Osmotic pressure ratio	2.5 to 2.6 (when 1g is dissolved in 10mL of water) (ratio to saline)
Indications	Neonatal convulsion/ status epilepticus
Dosage and administration (Neonatal convulsion)	Initial dose: 20 mg/kg of phenobarbital is administered intravenously. The dose should be adjusted according to the patient's condition within the range not exceeding the initial dose, and additional intravenous administration should be performed. Maintenance administration: 2.5 to 5 mg/kg of phenobarbital is intravenously administered once daily.
Usage precautions	Impaired consciousness, decreased blood pressure, and respiratory depression may occur, and so it is desirable to measure the blood concentration of this drug in order to appropriately adjust the dose.

Id. at 13.

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Z. Kou Kawada et al., *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*, 42(4) JPN. J. CLIN. PHARMACOL. THER. 205 (2011) ("Kawada 2011")

Kawada 2011 was published in 2011 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Kawada 2011 describes the clinical trial assessing the efficacy and safety of a new phenobarbital preparation for injection, NOBELBAR®, in Japan, specifically designed for safer use in neonates with seizures. Kawada 2011 at Abstract. Given the "instability of phenobarbital sodium in water," existing phenobarbital injection preparations often include "organic solvents such as benzyl alcohol and propylene glycol," which can be "hazardous to premature and neonatal infants." *Id.* at 205-06. Thus, there was a "strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives." *Id.* at 206. In response, a lyophilized product of phenobarbital sodium, entirely free of additives, was developed. *Id.* at 205-06. Since December 2008, the product has been marketed in Japan for the "treatment of neonatal seizures and status epilepticus" under the brand name "NOBELBAR® 250 mg for injection." *Id.* at 210.

The administration protocol began with phenobarbital being "administered intravenously at a loading dose of 20 mg/kg," followed by "an additional dose of 20 mg/kg . . . if the seizures did not resolve." *Id.* at Abstract. The "primary efficacy was evaluated 30 minutes after the administration of the loading dose." *Id.* Infants who responded to the initial loading dose "received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days." *Id.* NOBELBAR® was tested on "10 neonates with seizures," and the "primary efficacy was evaluated as complete response in all patients." *Id.* Adverse events were reported in "9 out of the 10 patients (90%), most of which were mild." *Id.*

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The study results demonstrated that NOBELBAR® "was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range." *Id.* Additionally, the study noted "no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug." *Id.* at 209-10. The findings clearly indicate that "the new phenobarbital preparation for injection (NOBELBAR®) is effective for the treatment of new neonatal seizures at the dosage examined in the present trial." *Id.* at 209.

AA. Joseph Herschel Kern, *Freeze Drying as a Method of Processing Some Pharmaceutical Products* (1954) (dissertation for Doctor of Philosophy, Ohio State University) ("Kern")

Kern was a dissertation that was approved in 1954 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Kern provides a comprehensive overview of the freeze-drying process, also known as "drying by sublimation" or "lyophilization," which involves "low temperature evaporation of water under vacuum following freezing." Kern at 2, 19. This method has gained significant importance in the pharmaceutical industry due to its ability to preserve biologicals and other perishable medications that otherwise would deteriorate or be wasted before their expiration date. *Id.* at 2-3. As Kern notes, "freeze drying has in many respects aided in overcoming some of these heretofor unsolved problems," minimizing waste by extending the shelf life of sensitive products. *Id.* at 3.

The freeze-drying process is a "reverse process of sublimation," where "the residue rather than the vapor is the product desired," particularly in pharmaceutical manufacturing, including antibiotics, vitamins, and blood plasma. *Id.* at 19. The procedure involves two main stages: first, the product is "frozen" and then subjected to high vacuum conditions to sublime the ice rapidly. *Id.* at 4. The primary advantage of this approach is that "the properties of labile substances are unchanged during drying," which allows for "prolonged preservation of desired characteristics

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during the storage period." *Id.* at 4. Furthermore, the solubility of products dried this way is "remarkably fast and complete," enhancing the usability and longevity of commercial labile products. *Id.*

The process begins with "pre-freezing," which can be achieved by external cooling or by "vacuum evaporation to induce 'self-freezing.'" *Id.* at 21-22. For medicinal products in small vials, freezing is often performed directly within vacuum chambers by lowering the temperature to as low as -40°C. *Id.* Following freezing, the drying process consists of two stages: "ice is evaporated from the frozen mass," and then "moisture is removed from the final dry solid leaving less than 0.5 per cent moisture in the finished product." *Id.* at 22-23. The required drying temperature varies depending on the product; for example, vitamin preparations dry at -5°C to -10°C, plasma at -20°C to -25°C, and antibiotics at -25°C to -32°C. *Id.* at 23.

Kern also discusses specific applications, such as the lyophilization of phenobarbital. Approximately 1 gram of phenobarbital was dissolved in buffer solutions, heated, cooled, and then "lyophilized." *Id.* at 81. Interestingly, it was noted that "freeze drying seems to reduce the wetability of phenobarbital." *Id.* at 107.

BB. Kung-Tien Liu & Chien-Hsin Chen, *Determination of Impurities in Pharmaceuticals: Why and How?, in* QUALITY MANAGEMENT AND QUALITY CONTROL - NEW TRENDS AND DEVELOPMENTS (Paulo Pereira & Sandra Xavier eds., 2019) ("Liu")

Liu was published on April 2019 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Liu focuses on the importance of managing "impurities, particularly the API-related impurities, i.e., degradation-related impurities (DRIs) and interaction-related impurities (IRIs)." Liu at Abstract. Liu defines impurities "any component of a drug substance that is not the chemical entity defined as the drug substance and in addition, for a drug product, any component that is not a formulation ingredient." *Id.* at 1 (internal citations omitted). Liu teaches

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that these impurities can arise from various sources, including "synthetic/manufacturing processes, degradation, storage conditions, container, excipients, or contamination" and that they can be "identified or unidentified, volatile or nonvolatile, organic or inorganic species." *Id.* Liu further teaches that impurities can be "generated by degradation of API itself under specific storage conditions, e.g., oxidation, dehydration, carbon dioxide removal, etc." or via "the interaction between API and excipients, container, or residual impurities in excipients, reagents, or solvents." *Id.* at 2-3. API-related impurities are of particular concern due to their potential "genotoxic, mutagenic, and carcinogenic risk[s]." *Id.*

Liu reviews international regulatory requirements for managing these impurities, emphasizing that the presence of impurities may "affect the quality, safety, and efficacy of drug products." *Id.* at 3. Liu notes that regulatory guidelines such as ICH Q3A(R2) require that any impurity present in an API at a level greater than the identification threshold must undergo studies to characterize its structure, even if it is a degradation product observed in stability studies. *Id.* at 4. Liu outlines a comprehensive approach to managing degradation products in drug substances and products, summarizing five major steps required by ICH Q3B(R2) for controlling these impurities:

1. Confirm which impurities are degradation products?
2. Monitor and/or specify the amount of all degradation products.
3. Summarize all degradation products during manufacture and stability studies.
4. Elucidate and justify a rational evaluation of possible degradation pathway in the drug product or interaction with excipients or container closure system.
5. Establish specifications of all degradation products, including specified identified, specified unidentified, unspecified degradation product with an acceptance criterion of not more than (≤) identification threshold described in Q3B(R2), and their total amount.

Id. at 4-5. Additionally, Liu discusses the concept of the threshold of toxicological concern ("TTC"), which "has been developed to define an acceptable intake for any unstudied chemical

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that poses a negligible risk of carcinogenicity or other toxic effects." *Id.* at 5. The TTC generally sets an exposure level of 1.5 μg per person per day for each impurity, a threshold considered to pose minimal safety concerns, particularly for genotoxicity and carcinogenicity. *Id.*

To establish analytical methods and acceptance criteria for PRIs and DRIs, Liu outlines several key steps, including (1) stress studies of APIs, (2) accelerated stability studies, and (3) long-term stability studies. *Id.* at 6; *see also id.* at Fig. 4.

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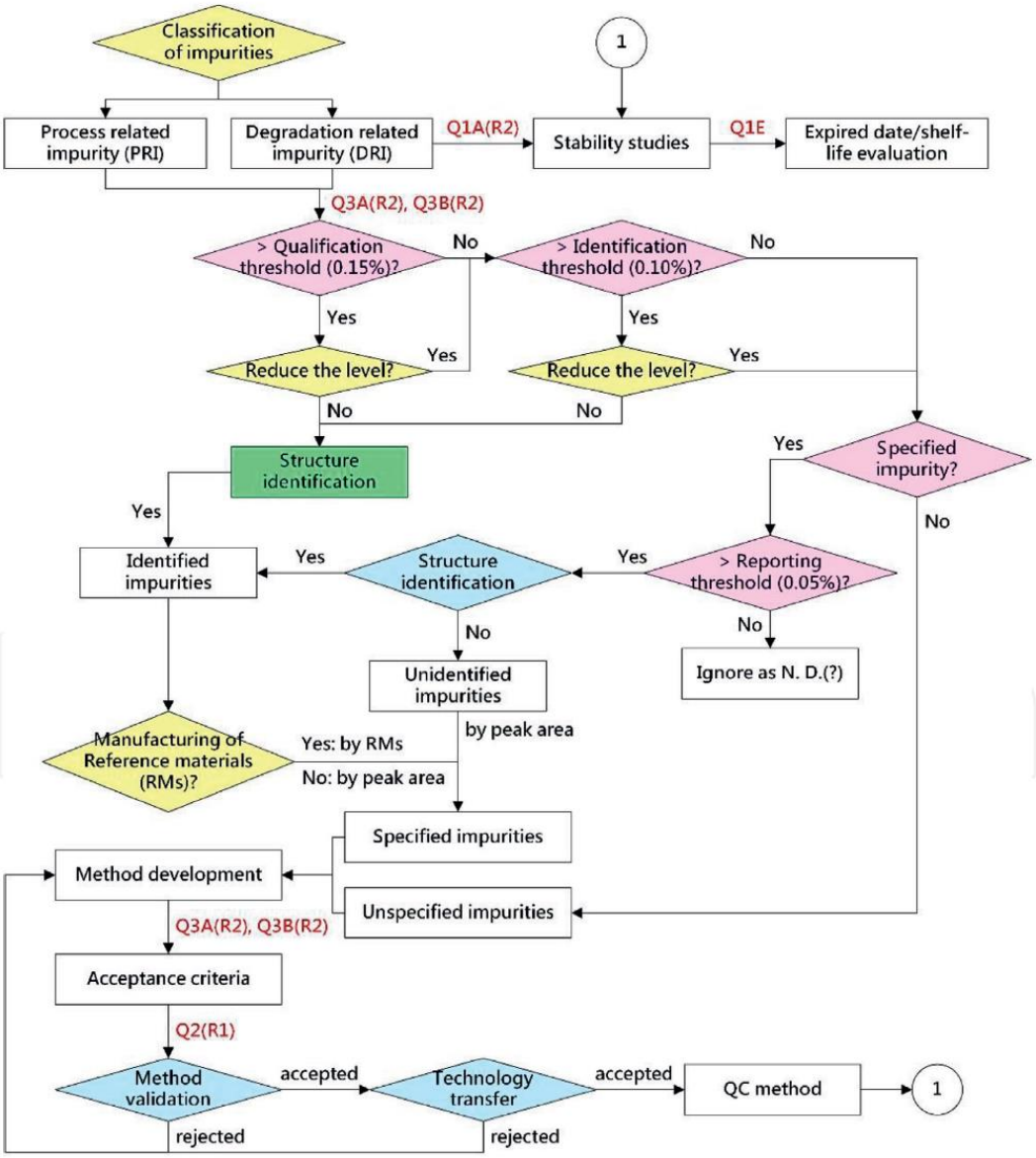


Figure 4.
Scheme to establish analytical methods and acceptance criteria of process-related impurities (PRIs) and degradation-related impurities (DRIs) according to the requirements of ICH guidelines [2, 3, 17, 22, 39, 40].

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Liu also discusses the importance of conducting impurity determination and forced degradation studies as tools for predicting potential impurities, developing analytical methods, and understanding storage conditions and the stability of drug products. *Id.* at 4. Ultimately, Liu states that "[m]anagement of impurities related to APIs in pharmaceutical products must be implemented in strict compliance with the regulatory requirements of pharmaceutical industry due to their quality and safety concerns." *Id.* at 14.

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CC. NOBELBAR® 250 mg for Injection Label ("Nobelbar Label")

Nobelbar 250 mg for Injection has been marketed in Japan since December 2008, and its label was published and publicly available as of that date, thus qualifying it as prior art to the Patents-in-Suit under 35 U.S.C. § 102. The Nobelbar Label discloses that one vial of the phenobarbital sodium freeze-dried preparation contains 274 mg of phenobarbital sodium (equivalent to 250 mg of phenobarbital) with no additives. *See* Nobelbar Label. The Nobelbar Label also discloses that when 1g of the product is dissolved in 10 mL of water, the pH ranges between 9.2 and 10.2. *Id.* The Nobelbar Label further discloses the indications for use as neonatal seizures and status epilepticus, with an initial intravenous dose of 20 mg/kg of phenobarbital for neonatal seizures and 15-20 mg/kg of phenobarbital for status epilepticus. *Id.* To prepare the product for intravenous administration, the Nobelbar Label teaches that one vial should be dissolved in 5 mL of water for injection or physiological saline. *Id.*

DD. Frauke Mattner & Petra Gastmeier, *Bacterial contamination of multiple-dose vials: A prevalence study*, 32(1) AM. J. INFECT. CONTROL 12 (Feb. 2004) ("Mattner")

Mattner was published in 2004 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Mattner conducted a prevalence study to investigate the use and contamination of multiple-use vials (MDVs) in a 1300-bed tertiary hospital. Mattner at Abstract. Infection control nurses collected all used MDVs from every ward, recording data on medication, labeling, storing temperature, and the dates of opening. *Id.* at Abstract, 13. Each vial was also tested for sterility. *Id.* Out of 227 vials collected from 47 wards, one vial and one spike were contaminated with *Staphylococcus epidermidis*, resulting in a contamination rate of 0.9% (95% CI, 0.3-2.1). *Id.* The study revealed that only 50% of the MDVs had their opening dates marked, 13% of which had expired, and only 19% were stored in a refrigerator. *Id.* at Abstract. The findings highlight the

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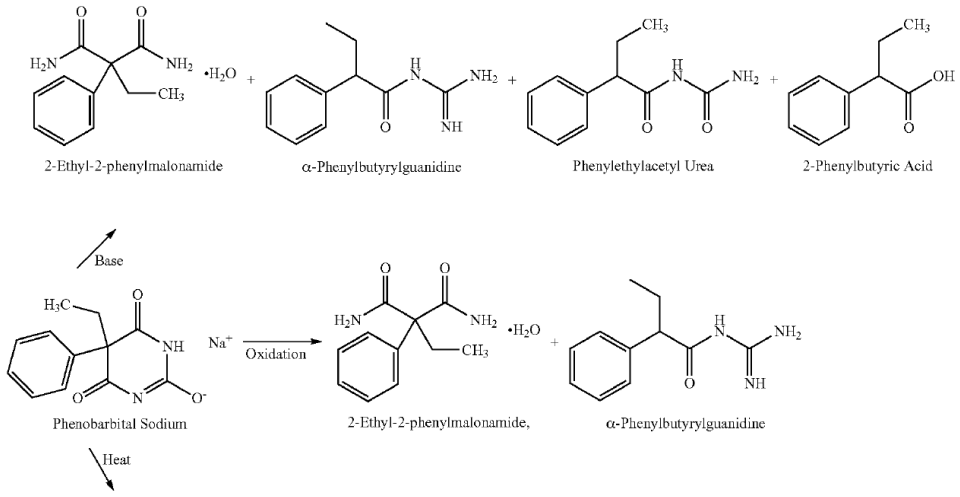
"somewhat risky handling" practices of MDVs, which pose potential infection risks. *Id.* at Abstract, 14.

EE. U.S. Patent Application Publication No. US 2017/0143719 ("Parker")

Parker was published on May 25, 2017 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Parker describes a "stable formulation of phenobarbital sodium injection" that minimizes impurity formation during extended storage. Parker at Title, Abstract. Parker addresses the issue that traditional phenobarbital sodium formulations, which are typically dissolved in water, can undergo hydrolysis, leading to the destruction of the phenobarbital ring complex and the formation of impurities such as phenyl ethyl acetyl urea (PEAU), phenyl butyric acid (PBA), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG):

TABLE 1

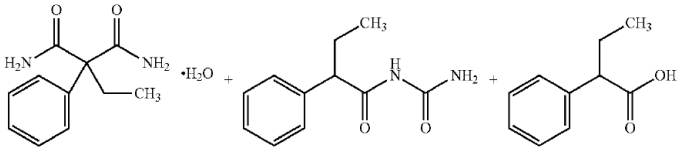
Degradation Products of Phenobarbital Sodium



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TABLE 1-continued

Degradation Products of Phenobarbital Sodium



Id. at [0004], [0006], Table 1. The presence of water in these formulations accelerates this degradation, contributing to the accumulation of these impurities. *Id.* at [0004], [0006], [0016].

To overcome these challenges, Parker introduces a phenobarbital sodium solution that is "extremely stable that do[es] not generate any significant amounts of impurities during extended storage." *Id.* at [0017]. This formulation includes "phenobarbital sodium in an amount of 15 to 200 mg/mL," a C1-C4 alcohol such as ethanol, and propylene glycol, with a pH "between 9 and 12," which is adjusted using a minimal amount of acid or base. *Id.* at Abstract, [0017], [0031], [0034], [0039]. The inclusion of a C1-C4 alcohol and propylene glycol, rather than water, helps to stabilize the phenobarbital sodium and prevent the formation of impurities. *Id.* at [0017], [0034]. The solution is designed to contain "no more than 50 mg/mL water," including any water introduced from the pH adjustment, significantly reducing the potential for hydrolysis and impurity formation. *Id.* at Abstract, [0039].

Notably, Parker's formulation achieves "no more than 0.8% of phenyl ethyl acetyl urea impurity as well as no detectable amount of phenyl butyric acid after two years storage at room temperature," demonstrating its stability over time. *Id.* at Abstract, [0017]. This represents a substantial improvement over previous formulations, which allowed for up to 10% PEAU and 1% PBA after similar storage conditions. *Id.* at [0006]. Additionally, the phenobarbital solutions are versatile, with a range of concentrations from "15 to 200 mg/mL" and preferred concentrations of "30 to 135 mg/mL," making them suitable for various clinical needs. *Id.* at [0031], [0036].

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Parker also details the preparation process, which involves dissolving phenobarbital sodium in the solvent mixture and adjusting the pH before filling appropriate containers, such as pre-filled syringes or vials, with "about 0.5 to about 20 mL of the solution." *Id.* at [0058], cls. 1, 10.

FF. Michael J. Pikal, *Freeze Drying*, *in* ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY VOL. 1, 1807-33 (James Swarbrick ed., 3rd ed. 2007) ("Pikal")

Pikal was published in 2007 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Pikal provides a detailed overview of the freeze-drying process, also known as lyophilization, which is extensively used in the pharmaceutical industry to convert solutions of labile materials into stable solids suitable for distribution and storage. Pikal at 1807-08. This process is particularly advantageous for the stabilization of sensitive drugs because it maintains sterility and minimizes exposure to contaminants. *Id.* at 1808.

The freeze-drying process involves several key stages. Initially, an aqueous solution containing the drug and various formulation aids, or "excipients," is filled into glass vials, which are then placed onto temperature-controlled shelves within a drying chamber. *Id.* at 1807. The objective of the freezing stage is "to remove most of the water from the system by formation of ice" and "to convert all solutes into solids, either crystalline solids or a glass." *Id.* at 1808. To achieve this, the shelf temperature is gradually reduced, typically to around -40°C, converting nearly all the water in the solution into ice. *Id.* at 1807.

Once the freezing stage is complete and all water and solutes have solidified, the system is evacuated by vacuum pumps to achieve a low pressure, typically in the range of 0.03–0.3 Torr. *Id.* at 1807. The temperature of the shelves is then increased to supply the necessary energy for sublimation, which begins the primary drying stage. *Id.* Primary drying aims to "remove the ice by direct sublimation," and this phase can take several days or even weeks, depending on the

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formulation and process design. *Id.* The conclusion of primary drying, marked by the removal of all ice, signifies the start of secondary drying. *Id.* Secondary drying is conducted at shelf temperatures in the range of 25-50°C, to desorb any remaining unfrozen water from the product. *Id.*

The advantages of freeze-drying over other drying methods, such as spray drying, are numerous. Freeze-drying is preferred for products intended for parenteral administration because it maintains the "sterility and particle free characteristics of the product" more effectively. *Id.* at 1808. Since the process involves sterile filtration immediately before filling into the final container and minimal human exposure during subsequent handling, it is easier to control sterility and prevent contamination compared to methods that require handling of dry powders. *Id.* Moreover, the ability to control moisture content and headspace gas when sealing vials in the freeze dryer is important for products whose stability is sensitive to residual moisture or oxygen. *Id.*

GG. Sakthivel Lakshmana Prabu & T.N.K. Suriyaprakash, *Impurities and Its Importance in Pharmacy*, 3(2) INT. J. PHARM. SCI. REV. RES. 66 (2010) ("Prabu")

Prabu was published in 2010 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Prabu discusses the importance of understanding and managing impurities in drug substances and products. *See generally* Prabu. Prabu teaches that according to the International Conference on Harmonisation (ICH) Guidelines, an impurity is defined as "any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances." *Id.* at 66. Prabu further teaches that definition extends to drug products, where any extraneous material not defined as the drug substance or an excipient is considered an impurity, even if it is inert or possesses superior pharmacological

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properties. *Id.* Prabu underscores that "[t]he impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention." *Id.*

Prabu elaborates on the sources of impurities, noting that "[m]ost active pharmaceutical ingredients (API) are produced by organic chemical synthesis," which can introduce residual solvents, inorganic components, and organic compounds as impurities. *Id.* Prabu further discloses that these impurities may arise from "starting materials, by-products and residual solvents from the API synthesis; degradants formed during the process and long-term storage; contaminants from packaging components and other drug products manufactured in the same facility." *Id.* at 66-67.

Prabu emphasizes the importance of isolating and characterizing impurities to accurately monitor them because "approximate estimations of impurities are generally made against the material of interest (i.e. drug substance) and can be incorrect" due to differences in structure and detector response. *Id.* at 68.

Finally, Prabu discusses the qualification of impurities, which involves "acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) being considered." *Id.* at 69. Prabu teaches that an impurity is considered qualified if it meets criteria such as not exceeding levels observed in an FDA-approved drug, being a significant metabolite, being justified by scientific literature, or not exceeding levels evaluated in genotoxicity studies. *Id.* The recommended qualification thresholds are outlined in ICH guidelines, ensuring that impurities are managed to maintain the safety and efficacy of pharmaceutical products. *Id.* at 69; Tables 3-4.

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Table 3: Drug substance impurities thresholds

Maximum daily dose[a+]	Reporting threshold[b,c]	Identification threshold[b,c]	Qualification threshold[b,c]
≤ 2g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is less)	0.15% or 1.0 mg/day intake (whichever is less)
≥ 2g/day	0.03%	0.05%	0.05%

a The amount of drug substance administered per day.
b Higher reporting threshold should be scientifically justified.
c Lower threshold can be appropriate if the impurities are unusually toxic.

Table 4: Thresholds for degradation products in drug products

Maximum daily dose[a]	Reporting threshold[b,c]
≤1 g	0.1%
>1 g	0.05%
Maximum daily dose[a]	**Identification threshold[b,c]**
<1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Maximum daily dose[a]	**Qualification threshold[b,c]**
<10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0. 2% or 3 mg TDI, whichever is lower
>2 g	0.15%

a The amount of drug substance administered per day.
b Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.
c Higher thresholds should be scientifically justified

HH. Dejan S. Przic et al., *Lyophilization — The Process and Industrial Use,* 58(12) CHEM. IND. 552 (2004) ("Przic")

Przic was published in 2004 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Przic defines lyophilization as a "stabilizing process in which the substance is first frozen and then the quantity of the solvent is reduced first by sublimation (primary drying) and then by desorption (secondary drying)." Przic at Abstract, 552-53. This process reduces the solvent content to levels that "will no longer support biological growth or chemical reactions," making it particularly valuable for pharmaceuticals and food products. *Id.* at Abstract. The process is extensively used in the healthcare industry for pharmaceuticals such as "chemical compounds, parenteral formulations, vaccines," and diagnostic products. *Id.* at 557, Table 1 (showing lyophilized materials in healthcare).

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Table 1. Materials that are lyophilized for use in healthcare

Product	Active Ingridient	Pharmacological Group
Lemod Solu®	Methylprednisolone	Corticosteroid
Hidrokortizon® (Hemol®)	Hydrocortisone	Corticosteroid
Azaran®	Ceftriaxone	Antibiotic
Fenobarbiton–Na®	Phenobarbitone	Antiepileptic
Nitroprusid–Na®	Nitroprusside	Vasodilator

With advancements in vacuum technologies, "reliable commercial freeze-dryers" have been developed, allowing the lyophilization method to become "fully integrated within the pharmaceutical industry." *Id.* at 552. The process is particularly beneficial for reducing "thermal inactivation of the product during freezing" and minimizing "oxidative denaturation" by sealing the product under vacuum or inert gas. *Id.* at 553.

The process begins with "dissolving the drug and excipients in a suitable solvent," typically water for injection (WFI), followed by "sterilizing the bulk solution" and "filling into individual sterile containers." *Id.* at 559. These containers, often glass vials or ampoules, are partially stoppered and transported to the lyophilizer under aseptic conditions. *Id.* at 553, 559. The solution is then frozen "by placing the partially stoppered containers on cooled shelves" or pre-frozen in another chamber. *Id.* at 559.

During the freezing stage, the principal functions are to "separate the solvent from the solutes," "minimize thermal degradation," "imnobilize [*sic*] the components in the solution," and "prevent product foaming when vacuum is applied." *Id.* at 554. Ideally, "prefreezing should result in the complete crystallization of both the solvent (usually) water and the solutes within the solution." *Id.* As freezing progresses, "water will form ice crystals," and solutes are confined to the interstitial regions between these crystals. *Id.*

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Once the solution is fully frozen, "the pressure in the freeze-dryer is reduced, and heat is applied to the formulation to initiate sublimation of the ice crystals." *Id.* at 555. The primary drying process continues until all ice is removed, leaving only water adsorbed to the bulk powder or structurally integrated with the solute. *Id.* at 555-56. Secondary drying follows, where "moisture content in the product" is further reduced by desorption without reducing the volume of the interstitial cake, achieving a water content of "2% or less." *Id.* at 556. Przic discloses comparative drying times and temperatures for drying processes as well as process times of a typical pharmaceutical lyophilization process:

Table 2. Temperatures and drying times for drying processes

Process		Typical Operating Temperatures	Drying Times
Spray Drying		80–100°C	< 10 min
Fluid Bed Drying		80°C	< 100 min
Freeze drying (1 cm product depth)	Milk	– 5°C	600 min
	Blood Serum	– 25°C	1200 min
	Cytomegalovirus Vaccine	– 40°C	3600 min

Table 3. Process time of a typical pharmaceutical or biotechnology lyophilization process

Process phase	Time
Filling and loading 37,000 vials at 120 vials/min	6 h
Freezing (ambient to –40°C)	12 h
Primary drying process	48 h
Secondary drying process	24 h
Backfilling and stoppering	1 h
Total process time	91 h

Id. at Tables 2-3.

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After lyophilization, the formulation is typically protected from the environment by "stoppering the container" within the freeze-dryer, which is important to maintaining stability. *Id.* at 556.

Przic also emphasizes the importance of container design, noting that "containers must be regarded as an integral part of the processing equipment" due to their influence on heat transfer and vapor flow. *Id.* at 553.

Finally, Przic discloses a typical flowchart of the pharmaceutical application of lyophilization used for manufacturing parenteral products in vials:

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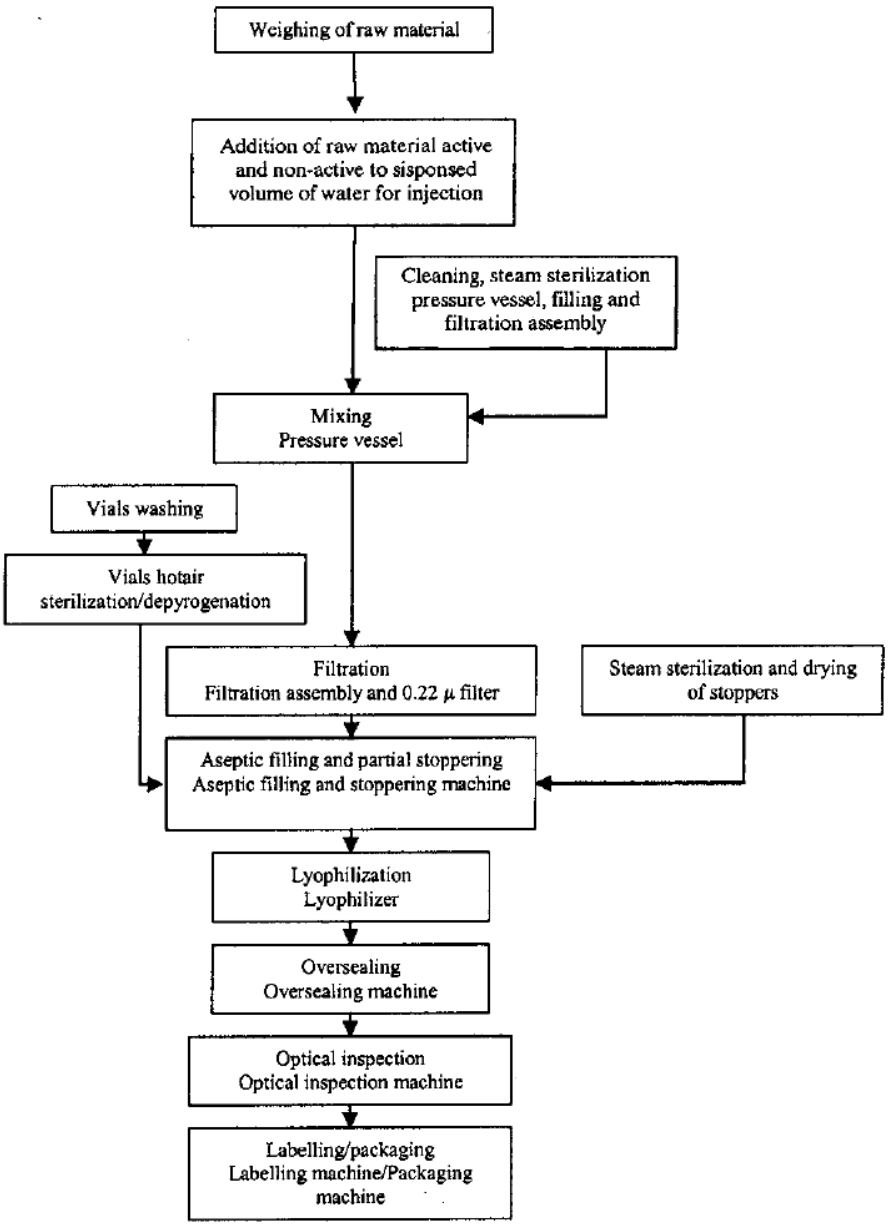


Figure 6. Typical flowchart of the pharmaceutical application of lyophilization – courtesy of the Hemofarm Group

Id. at Fig. 6.

II. FREEZE-DRYING/LYOPHILIZATION OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS (Louis Rey & Joan C. May eds., 3d ed. 2010) ("Rey")

Rey was published in 2010 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Rey provides an overview of the lyophilization process of pharmaceutical and biological

products. The process begins with the "freezing step," where the material is "hardened by low temperatures." Rey at 2. This initial cooling typically occurs at atmospheric pressure, sometimes in a separate cabinet. *Id.* at 16. As the shelf temperature continues to drop, it can reach as low as -50°C, ensuring the material is thoroughly frozen. *Id.* at 54.

Following freezing, the "sublimation phase or primary drying" takes place, where the "frozen material, placed under vacuum, is progressively heated" to provide enough energy for the ice to sublimate. *Id.* at 3. Primary drying is carried out under vacuum conditions to facilitate the sublimation process, which removes most of the water content from the product. *Id.* at 16.

Once all the ice has sublimated, the process enters the "desorption phase or secondary drying," which starts when "ice has been distilled away." *Id.* at 3. This phase requires a higher vacuum and an increase in temperature to above zero, which helps extract the remaining bound water. *Id.* at 16. The challenge in this phase is to achieve the right level of residual moisture, as both "overdrying" and "underdrying" can negatively affect the product. *Id.* at 3. Typically, the goal is to reach a final "very low" residual moisture content of "less than 2%" in the lyophilized product, with levels usually falling between 0.5% to 4%. *Id.* at 451.

The lyophilization process is particularly advantageous for the pharmaceutical industry because it allows for the drying of products "under sterile conditions," making it suitable for injectable formulations. *Id.* at 269, 441. Sterility is maintained by sterile filtering the solutions, aseptically filling them into containers, and then freeze-drying. *Id.* at 258, 269. This ability to run under sterile conditions is a significant benefit, as it minimizes contamination risk and maintains product integrity. *Id.* at 441.

The long-term benefit of lyophilization is seen during storage, "due to the removal of water, which facilitates many chemical degradation processes, as well as immobilization of the

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molecule." *Id.* at 82. By reducing water activity to an optimal level, the process helps preserve the product's stability and effectiveness over time. *Id.* at 242.

JJ. Ramesh alli Sandhyarani G, *Development and Evaluation of Lyophilized Product of Apo-Acetozolamide*, 6(9) IOSR J. PHARM. 48 (2016) ("Sandhyarani")

Sandhyarani was published in 2016 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Sandhyarani focuses on the development and evaluation of a lyophilized product of Apo-Acetazolamide. Sandhyarani describes a process known as "lyophilization or freeze drying," which "involves the removal of water or other solvent from a frozen product by a process called sublimation followed by desorption." Sandhyarani at Abstract. This technique is particularly relevant for creating "freeze-dried products for parenteral use," commonly referred to as "Powders for injection or infusion." *Id.*

The manufacturing procedure for lyophilized Apo-Acetazolamide involves several steps. First, the required batch size of Water for Injection is collected in a stainless steel vessel and cooled to a temperature of 4-8°C. *Id.* at 51. 80% of this cooled water is then transferred to another stainless steel vessel, where a weighed quantity of Acetazolamide is added with continuous stirring until a clear solution is obtained. *Id.* The pH of the solution is checked and adjusted to 9.6 using 1N NaOH. *Id.* Once the solution reaches the desired batch size with Water for Injection, the final pH is confirmed and adjusted if necessary. *Id.*

After preparing the solution, it is filtered through a 0.2µ membrane filter to ensure sterility. *Id.* The filtered solution is then filled into 10mL USP Type I clear glass vials, which are half stoppered with double-slotted chlorobutyl rubber stoppers. *Id.* These vials are then loaded for lyophilization following an optimized lyophilization cycle:

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LYOPHILIZATION CYCLES

TRIAL1

PRECOOLING

SL.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180

PRIMARY DRYING

SL.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)	PRESSURE (µbar)
1	-32	60	900	150
2	-10	60	480	150
3	0	60	120	150

CYCLE 2

PRECOOLING

SL.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180
3	-30	30	45
4	-45	30	120

PRIMARY DRYING

SL.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)	PRESSURE (µbar)
1	-32	120	900	250
2	-10	30	300	100
3	0	120	300	150

SECONDARY DRYING

SL.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION	PRESSURE (µbar)
1	10	60	180	50
2	30	30	180	50
3	40	20	600	50

OBSERVATION: The moisture content observed was 10.1%.

To reduce the water content a new modified cycle was taken in the next trial.

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CYCLE 3

PRECOOLING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180

PRIMARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION (MIN)	SOAK DURATION (MIN)	PRESSURE (µbar)
1	-25	120	300	250
2	-10	30	900	100
3	0	120	600	150

SECONDARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION	PRESSURE (µbar)
1	10	60	240	50
2	30	30	240	50
3	40	20	240	50

OBSERVATION

- The moisture content was found to be 8.4%

CYCLE 4

PRE-COOLING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180
3	-30	30	45
4	-45	30	120

PRIMARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)	PRESSURE (µbar)
1	-25	120	300	250
2	-10	30	300	100
3	0	120	300	150

SECONDARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION	PRESSURE (µbar)
1	10	60	240	50
2	30	30	240	50
3	40	20	240	50

OBSERVATION

- The moisture content was found to be 6.36%.

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CYCLE 5

PRE-COOLING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180

PRIMARY DRYING

Ss.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)	PRESSURE (µbar)
1	-30	120	300	250
2	-25	100	590	150
3	-15	10	600	100
4	0	120	600	150

SECONDARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION	PRESSURE (µbar)
1	10	60	240	50
2	30	30	240	50
3	40	20	240	50

OBSERVATION

- The moisture content was found to be 5.7%And time taken by the cycle is 67.80hrs=2.8days.

  To reduce the cycle duration a new modified cycle was taken in the next trial.

CYCLE 6

PRE-COOLING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)
1	-25.0	90	60
2	-45.0	90	180

PRIMARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION(MIN)	PRESSURE (µbar)
1	-30	120	300	250
2	-25	120	590	150
3	-15	10	600	100
4	0	120	300	100

SECONDARY DRYING

S.NO	FINAL T(°C)	RAMP DURATION(MIN)	SOAK DURATION	PRESSURE
1	10	60	240	50
2	30	30	240	50
3	40	20	240	50

OBSERVATION

- The moisture content was found to be 4.3% and the cycle time was reduced to 62.3 hrs from 67.80hrs.

Id. at 51, 54-58 Upon completion of the lyophilization process, the vials are stoppered under vacuum and sealed with aluminum flip-off seals to maintain sterility and stability. *Id.* at 51.

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The lyophilized Apo-Acetazolamide is later reconstituted with "0.9% sodium chloride injection." *Id.* at 59.

KK. James E Silberzweig et al., *Society of Interventional Radiology position statement on injection safety: improper use of single-dose/single-use vials*, 24(1) J. VASC. INTERV. RADIOL. 111 (2013) ("Silberzweig")

Silberzweig was published in 2013 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Silberzweig emphasizes the importance of safe injection practices when administering medication from a single-dose vial (SDV) or single-use vial. Silberzweig at 111. Silberzweig discloses that "[m]edication from an SDV is intended for parenteral administration for a single patient during a single procedure." *Id.* Additionally, Silberzweig teaches that "[t]he preservative agents [found in multiple-dose vials (MDVs)] has no effect on viruses and does not protect against contamination when healthcare personnel fail to follow safe injection practices." *Id.*

LL. Małgorzata Sznitowska et al., *The physical characteristics of lyophilized tablets containing a model drug in different chemical forms and concentrations*, 62(1) ACTA POLONIAE PHARM. 25 (2009) ("Sznitowska")

Sznitowska was published in 2009 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Sznitowska examines phenobarbital and phenobarbital sodium as model drugs. Sznitowska at Abstract, 25. The study highlights that tablets containing phenobarbital in the form of sodium salt exhibited "better mechanical strength" compared to those prepared with the "water-insoluble phenobarbital–acid form." *Id.* at Abstract. Furthermore, the mechanical characteristics of these tablets indicate that "plasticity and porosity were reduced when sodium phenobarbital was incorporated at a higher dose." *Id.*

Sznitowska underscores the importance of developing alternative drug formulations for populations that have difficulty swallowing traditional tablets and capsules, such as children and the elderly. *Id.* at 25. It is noted that "50% of population is affected by this problem," leading to

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non-compliance and ineffective therapy. *Id.* To address this, orodispersible forms—such as "FMTs (fast-melting tablets), ODT (orally disintegrating tablets) or FDDF (fast dissolving/disintegrating dosage forms)"—are suggested, as they can "rapidly disperse or dissolve in the saliva" when placed in the mouth, allowing for easier swallowing. *Id.*

Sznitowska outlines three major methods for manufacturing these fast-dissolving tablets: "1) freeze-drying, 2) moulding by compression or heat-moulding, 3) direct compression." *Id.* Among these, "freeze-dried tablets" are noted to disintegrate faster in the oral cavity due to their high porosity. *Id.* This method was used in the study, where samples were "frozen at - 45°C and kept at this temperature for 60 minutes." *Id.* at 26. Primary drying was conducted for 40 hours at 0.08 mbar pressure with a gradual increase in shelf temperature to 20°C, followed by secondary drying where the temperature was raised to 35°C for 2 hours. *Id.*

Additionally, the stability of tablets containing phenobarbital or its sodium salt was tested under different storage conditions. The tablets were "placed in a hygrostat and stored at relative humidities (RH) 45%, 60% and 90%" over sulfuric acid solutions for four weeks. *Id.* The study also explored the pH levels of the drug solutions, noting that the pH of phenobarbital sodium solutions ranged from 7.6-9.2, while the pH of phenobarbital dispersions was 5.1. *Id.*

MM. Frederick Tishler et al., *Mechanism of Phenobarbital Degradation*, 51(3) J. PHARM. SCI. 214 (1962) ("Tishler")

Tishler was published in 1962 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Tishler discloses phenylethylacetylurea (PEAU) as a degradant of phenobarbital. Tishler at Abstract. Tishler further explains that PEAU was prepared by the thermal degradation of a 5% aqueous solution of phenobarbital, followed by the isolation of the resulting precipitate. *Id.* at 214.

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NN. Edward H. Trappler, *Freeze Drying, Scale-Up Considerations, in* ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY VOL. 1, 1834-49 (James Swarbrick ed., 3rd ed. 2007) ("Trappler")

Trappler was published in 2007 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Trappler outlines key lyophilization steps, processing parameters, and conditions. Trappler presents processing parameters for model presentation:

Table 1 Lyophilization process description: model presentation

Step	Processing parameters
Loading	Soak at 5°C (±5°) and 1 atm for 2 hr
Freezing	Ramp shelf to −40°C at an average controlled rate of 30°C/hr Control shelf at target set point of −40°C (±5°) for 3 hr
Primary drying	Evacuate chamber, control at a target set point of 80 μHg (±20 μHg). Ramp shelf to −10°C at an average controlled rate of 30°C/hr Control shelf at target set point of −10°C (±5°) for 15 hr
Secondary drying	Control chamber pressure at a target set point of 80 μHg (±20 μHg). Ramp shelf to 30°C at an average controlled rate of 30°C/hr Control shelf at target set point of 30°C (±5°) for 5 hr
Stoppering	Control chamber pressure at a target set point of 1 atm Control shelf at target set point of 30°C (±5°C).

Id. at Table 1.

Trappler also provides a "[l]yophilization process control recipe" using lysozyme as a model, including specific details on shelf temperature, pressure, and time for each stage of the process:

Table 2 Lyophilization process control recipe: lysozyme model presentation

	Process conditions		
Step	Shelf temperature	Pressure	Segment time
Loading	Soak: 5°C	atm	2 hr
Freezing	Ramp: 30°/hr	atm	1.5 hr
	Soak: −40°C	atm	3 hr
Primary drying	Ramp: 30°C/hr	80 μHg	1 hr
	Soak: −10°CC	80 μHg	15 hr
Secondary drying	Ramp: 30°C/hr	80 μHg	0.6 hr
	Soak: 30°C	80 μHg	5 hr
Stoppering	Soak: 30°C	atm	Total: 27.2 hr

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Id. at Table 2.

Furthermore, Trappler discloses "[c]ritical process parameter boundary conditions for a proven acceptable range" for each process conditions:

Table 5 Critical process parameter boundary conditions for a proven acceptable range

Process condition	Product loading	Cooling rate	Freezing	Primary ramp	Primary drying	Secondary ramp	Secondary drying
Shelf temperature:							
High	10°C	0.5°C/hr	−35°C	0.5°C/hr	−5°C	0.5°C/hr	35°C
Target	5°C	0.5°C/hr	−40°C	0.5°C/hr	−10°C	0.5°C/hr	30°C
Low	0°C	0.5°C/hr	−45°C	0.5°C/hr	−15°C	0.5°C/hr	25°C
Chamber pressure:							
High	atm	atm	atm	100 µHg	100 µHg	100 µHg	100 µHg
Target				80 µHg	80 µHg	80 µHg	80 µHg
Low				60 µHg	60 µHg	60 µHg	60 µHg
Time:	2 hr		3 hr		15 hr		5, 7, and 9 hr

Id. at Table 5.

OO. USP 40 — NF 35: The United States Pharmacopeia and National Formulary Vol. 1, U.S. Pharmacopeial Convention (2017) ("USP")

USP was published in 2017 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. USP provides detailed specifications for phenobarbital and phenobarbital sodium, highlighting their physical properties, stability, and storage requirements. Phenobarbital is described as "[w]hite, odorless, glistening, small crystals, or white, crystalline powder," which may exhibit polymorphism and is "stable in air." USP at 2493. It has a saturated solution with a pH of about 5 and is "[s]oluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates," but only "sparingly soluble in chloroform" and "very slightly soluble in water." *Id.*

Phenobarbital sodium, on the other hand, appears as "[f]laky crystals, or white, crystalline granules, or white powder," which is "odorless, has a bitter taste, and is hygroscopic." *Id.* Its solutions are "alkaline to phenolphthalein TS" and decompose on standing. *Id.* It is "[v]ery

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soluble in water; soluble in alcohol; practically insoluble in ether and in chloroform." *Id.* The pH of a phenobarbital sodium solution is between "9.2 and 10.2." *Id.* at 5665-66.

The monograph of phenobarbital specifies that it should contain "not less than 98.0 percent and not more than 101.0 percent of $C_{12}H_{12}N_2O_3$, calculated on the dried basis." *Id.* at 5663. It is chemically known as "2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-" or "5-Ethyl-5-phenylbarbituric acid." *Id.* It must be preserved "in well-closed containers" to maintain its stability. *Id.*

Similarly, the monograph for phenobarbital sodium indicates that it should contain "not less than 98.5 percent and not more than 101.0 percent of $C_{12}H_{11}N_2NaO_3$, calculated on the dried basis." *Id.* at 5665-66. It is identified as "2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-, monosodium salt" or "Sodium 5-ethyl-5-phenylbarbiturate." *Id.* It should be stored "in tight containers" to prevent moisture absorption, given its hygroscopic nature. *Id.*

The monograph for phenobarbital sodium injection describes it as a "sterile solution of Phenobarbital Sodium in a suitable solvent." *Id.* at 5666. The injection must contain "not less than 90.0 percent and not more than 105.0 percent of the labeled amount of $C_{12}H_{11}N_2NaO_3$." *Id.* The pH for this solution is also maintained between "9.2 and 10.2," and it is recommended to be stored "in single-dose or multiple-dose containers, preferably of Type I glass." *Id.*

PP. Material Safety Data Sheet: Phenobarbital Sodium Injection, USP, West-Ward Pharmaceuticals (Oct. 25, 2011) ("West-Ward")

West-Ward was published in 2011 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. West-Ward is a material safety data sheet for phenobarbital sodium injection, USP. West-Ward provides detailed composition information, listing phenobarbital sodium as comprising 6.5-13 wt. %, benzyl alcohol less than 2 wt. %, ethyl alcohol 7-9 wt. %, propylene glycol 68-79 wt. %, and water over 7 wt. %. West-Ward at §2. The physical and chemical

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properties section describes the injection as a colorless, aqueous solution with a pH range of 9.2 to 10.2. *Id.* at §9.

QQ. Lian Yu, *Amorphous pharmaceutical solids: preparation, characterization and stabilization*, 48 ADV. DRUG DELIV. REV. 27 (2001) ("Yu")

Yu was published in 2001 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102. Yu describes that "an amorphous solid may have short-range molecular order . . . but unlike a crystalline solid, an amorphous solid has no long-range order of molecular packing or well-defined molecular conformation if the constituent molecules are conformationally flexible." Yu at 27; *see also id.* at 30 ("Amorphous solids are not random at the molecular level, but may possess short-range order, residual crystallinity, polymorphic states, and regions of different density. . . . The structure of an amorphous solid is usually described as possessing crystal-like short-range molecular arrangement, but lacking long-range order."). Yu explores the production and properties of amorphous solids, which can be generated through common pharmaceutical processes such as melt quenching, freeze-drying, spray-drying, milling, and wet granulation. *Id.* at Abstract. Yu notes the pharmaceutical significance of amorphous solids, including "higher solubility, higher dissolution rate, and sometimes better compression characteristics than corresponding crystals." *Id.* at 27. However, "[a]morphous solids are generally less stable physically and chemically than corresponding crystals." *Id.* Yu further explains that amorphous solids are often produced through methods like rapid precipitation or freeze-drying, with "rapid freezing favor[ing] the formation of an amorphous solute, whereas introducing an annealing step may promote crystallization." *Id.* at 29. Moreover, Yu describes commonly used techniques such as X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), and solution calorimetry, which are employed to assess the degree of crystallinity in these materials. *Id.* at 31, Table 1.

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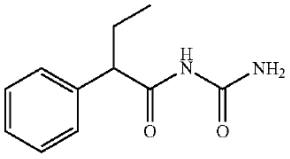
RR. U.S. Patent No. 11,857,683 ("Shah")

Shah issued on January 2, 2024 from Appl. No. 17/715,491 filed on April 7, 2022. Shah claims the benefit of U.S. Provisional Patent Application No. 63/319,918, filed on March 15, 2022. The named inventors of Shah are Malay Shah, Bhushan Borole, Ravi Patel, and Ajay Jaysingh Khopade. Because Shah was effectively filed on March 15, 2022—before the effective filing date of the '076 Patent, *see supra* Section III.B.4— and because it names another inventor from the '076 Patent, Shah is prior art to the '076 Patent under 35 U.S.C. § 102(b).

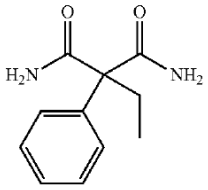
Shah discusses the stabilization of phenobarbital sodium for injection through the development of a "lyophilized pharmaceutical composition" that addresses the hydrolytic instability of phenobarbital and its salts. Shah at Title, Abstract, 1:14-25. Shah focuses on a composition that includes phenobarbital or its salts, such as phenobarbital sodium, and incorporates ethanol in a concentration range from "about 5000 ppm to about 70000 ppm" to enhance stability and reduce impurity formation. *Id.* at Abstract, 3:3-10, 5:6-11, 6:65-67.

A primary challenge with phenobarbital compositions is their "instability due to hydrolysis," which leads to a higher level of impurities. *Id.* at 1:33-42. These impurities can include various degradation products like "2-phenyl-2-ethyl acetyl urea, 2-phenyl-2-ethyl-malonamide, α-phenylbutyrylguanidine, 2-phenylbutyric acid and 5-methyl-5-phenylbarbituric acid":

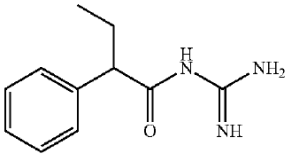
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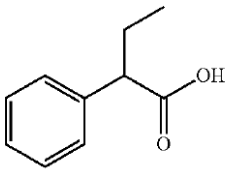
2-phenyl-2-ethyl acetyl urea



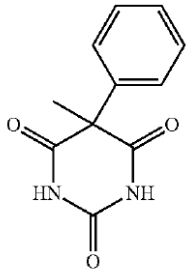
2-phenyl-2-ethyl-malonamide



α-phenylbutyrylguanidine



2-phenylbutyric acid



5-methyl-5-phenylbarbituric acid

Id. at 5:32-6:20, 6:47-50. To mitigate these issues, Shah suggests a formulation that utilizes a lower pH and a mixture of solvents such as alcohol and propylene glycol. *Id.* at 1:43-47.

The lyophilized composition of phenobarbital sodium described in Shah demonstrates stability over a lengthy shelf life, with the total impurities remaining below 0.5% after 36 months of storage at 20-25°C, and in some cases, not exceeding 0.2%. *Id.* at 3:61-67, 9:64-10:2. This stability is achieved without generating "any significant amount of impurities during extended storage," making it suitable for pharmaceutical applications. *Id.* at 2:39-45, 9:62-63.

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The invention allows for the preparation of a reconstituted aqueous solution for injection from the lyophilized composition, which remains stable and maintains low impurity levels. *Id.* at 6:29-32. Phenobarbital or its salts are included in concentrations ranging from "10-200 mg/ml." *Id.* at 6:57-64.

SS. U.S. Patent Application Publication No. US 2021/0085608 ("the '608 Publication")

The '608 Publication was published on March 25, 2021 and is therefore prior art to the '076 Patent under 35 U.S.C. § 102(a). *See supra* Section III.B.4.

The '608 Publication discloses "compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water." '608 Publication at [0002]. As described in the Detailed Description section, phenobarbital sodium has an IUPAC (International Union of Pure and Applied Chemistry) name of "sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$." *Id.* at [0072].

In the Background section, the '608 Publication describes prior art compositions of phenobarbital sodium. *Id.* at [0005]-[0009]. The '608 Publication indicates that "Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic" and that it is "typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent." *Id.* at [0005] (citing Parker, which is "a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol"). The '608 Publication notes the stability of solubilized phenobarbital sodium as a "recurring problem" as it "readily hydrolyzes in water forming various [toxic] degradation products," including "Phenobarbital Sodium forms the degradation

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products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG).” *Id.* at [0005]-[0006]. The ’608 Publication describes previous efforts to decrease the formation of toxic degradation products in the phenobarbital sodium formulations, including Parker, which “focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products,” but “impurities [in Parker’s liquid formulation] such a PEAU are still present in undesirable amounts, particularly after extended storage.” *Id.* at [0007].

The ’608 Publication indicates that the present invention provides compositions of and methods of producing “amorphous lyophilized Phenobarbital Sodium with high stability and purity,” disclosing that the lyophilized composition may include “no less than 98% Phenobarbital Sodium” and that the amorphous composition is “a storage-stable form of lyophilized Phenobarbital Sodium.” *Id.* at [0010], [0104]. The ’608 Publication states that the “[t]he quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products” and that “the stability of this formulation is superior to that of current commercial products.” *Id.* at [0011].

The ’608 Publication discloses that “[p]referably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%” and “[a]lternatively, the percentage of the lyophilized formulation that is amorphous can be 100%.” *Id.* at [0012]. Moreover, the ’608 Publication further states that “the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012].

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In typical embodiments, the ’608 Publication indicates that “the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg” and that it can be administered as “intramuscular injection or intravenous injection.” *Id.* at [0025], [0099]; *see also id.* at [0106].

With regard to the allegedly inventive process for preparing the storage-stable form of lyophilized Phenobarbital Sodium composition, the ’608 Publication discloses that the process includes “adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution.” *Id.* at [0013]; *see also id.* at [0075], [0077]. To adjust the pH of the phenobarbital sodium solution, the ’608 Publication suggests using hydrochloric acid (HCl) or Sodium Hydroxide (NaOH). *Id.* at [0015], [0077]. The ’608 Publication also notes that “[i]n preferred embodiments, the Water for Injection is sparged with nitrogen [for at least 30 minutes] prior to adding the Phenobarbital Sodium” and “[i]n additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.” *Id.* at [0014]; *see also id.* at [0075]. The ’608 Publication further discloses filtering the phenobarbital sodium solution prior to lyophilization. *Id.* at [0018]; *see also id.* at [0078].

The lyophilized phenobarbital sodium can be reconstituted in “either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration.” *Id.* at [0101], [0119]. Once the lyophilized phenobarbital sodium has been reconstituted after storage, the ’608 Publication discloses that the solution has “no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG.” *Id.* at [0024]. The ’608 Publication further discloses:

> Typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.1% PEAU when reconstituted in an aqueous

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> solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months both at RT and accelerated stability conditions. More typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.). Additionally, or alternatively, the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and accelerated stability conditions.

Id. at [0016]. The '608 Publication discloses that "the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT," wherein "the stability of the lyophilized Phenobarbital Sodium is determined by reconstituting the lyophilized Phenobarbital Sodium in an aqueous solution and measuring the amount of or the presence of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)." *Id.* at [0017]; *see also id.* at [0071], [0091]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication, upon reconstitution, "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]; *see also id.* at [0088]-[0090].

The '608 Publication discloses that "[d]epending on the desired amount of the lyophilized Phenobarbital Sodium product, the Phenobarbital Sodium solution may be lyophilized in any amount or the solution may be aliquoted into sterile containers (e.g., vials)." *Id.* at [0079]. The '608 Publication also teaches aliquoting phenobarbital sodium into single use dose vials for lyophilization. *Id.* at [0079] ("[T]o produce 65 mg or 130 mg doses of lyophilized Phenobarbital

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Sodium, a batch may be dissolved, mixed, pH adjusted if necessary, and filtered and then aliquoted into single use dose vials for lyophilization.").

In Tables 2 and 3, the '608 Publication compares the disclosed 65 mg and 130 mg lyophilized phenobarbital sodium that was reconstituted in water to the marketed 65 mg and 130 mg liquid phenobarbital sodium for injection USP (Westward Pharmaceuticals):

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TABLE 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder

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

CCVS: Clear Colorless Viscous Solution;

CCS: Clear Colorless Solution;

WLP: White Lyophilized powder

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

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

ND: Not Detected

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

PBG: α-phenylbutyrylguanidine,

PEAU: phenylethylacetylurea or Pheneturide

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

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

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TABLE 3

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation

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

CCVS: Clear Colorless Viscous Solution;
CCS: Clear Colorless Solution;
WLP: White Lyophilized powder
$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.
BQL: Below Quantitation Limit; (QL-0.05%);
ND: Not Detected
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-phenylbutyrylguanidine,
PEAU: phenylethylacetylurea or Pheneturide
*pH for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution
**The samples were stored at 30 ± 2° C., 65% RH ± 5

Id. at Tables 2 and 3. The '608 Publication notes that "the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration." *Id.* at 7.

The '608 Publication also discloses

- the stability data of Phenobarbital Sodium for Injection, 200 mg/vial, reconstituted in 10 mL of Water for Injection (Table 7);
- the stability data of Phenobarbital Sodium for Injection, 200 mg/vial, along with 90 mg of Sodium Chloride reconstituted in 10 mL of Water for Injection (Table 8); and
- the stability data of Phenobarbital Sodium for Injection, 130 mg/vial, reconstituted in 20 mg/mL of Water for Injection (Table 9):

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TABLE 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

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

TABLE 7-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

		Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
Test	Spec.	Jun. 5, 2020	2-8° C.	RT
Note Book Reference		192045-163 to 189	192045-163-183	

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

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TABLE 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)

Test	Specification	Initial	Reconstituted Solution Stability after 20 hrs	
			2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0-105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5%	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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

TABLE 9

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)

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

TABLE 9-continued

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)

Tests	Shelf life Specifications	Initial	Time 2 hrs 2-8 C.	2 hrs RT	4 hrs 2-8 C.	4 hrs RT	24 hrs 2-8 C.	24 hrs RT
Any unspecified degradation product @ RRT 0.37	NMT 0.2%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	NMT 1.5%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	To be reported	158	NP	NP	NP	NP	159	158

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

Id. at Tables 7-9. The '608 Publication also discloses

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- six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 10);
- six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (Table 11)[7];
- three months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial (Table 12);
- three months of stability data for Phenobarbital Sodium for Injection, 200 mg/vial (Table 13); and
- six months of stability data for Phenobarbital Sodium for Injection, 100 mg/vial (Table 16).

Id. at Tables 10-13, 16. The room temperature ("RT") and accelerated ("ACC") stability conditions were set at 25°C with 65% relative humidity ("RH") and 40°C with 75% RH, respectively. *Id.*; *see also id.* at [0103].

TABLE 10

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

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

[7] The Applicant repeated the same six months of stability data for Phenobarbital Sodium for Injection, 65 mg/vial (as shown in Table 10) for Table 11.

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TABLE 10-continued

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

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

TABLE 11

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

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

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

TABLE 12

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

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TABLE 12-continued

API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024		
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay Phenobarbital Sodium	90.0-105.0	100.1	98.1	101.0
Related Substances (% Area)	NMT 0.2%	ND	ND	ND
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.09	0.09
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051-84 to 122	

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

TABLE 13

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch#NPH2031A Fill Volume: 2.1 mL	Date Manufactured: Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear		Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);		Jun. 9, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024		
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6
Related Substances (% Area)	NMT 0.2%	BQL	ND	ND
2EPMM				

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TABLE 13-continued

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

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

TABLE 16

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

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

TABLE 16-continued

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

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

Id. at Tables 10-13, 16.

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The ’608 Publication further describes lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial, and 200 mg/vial:

TABLE 15

Lyophilization Cycle parameters.

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

TABLE 15-continued

Lyophilization Cycle parameters.

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

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

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

Id. at [0123], Table 15.

VII. THE CLAIMS OF THE PATENTS-IN-SUIT ARE INVALID FOR OBVIOUSNESS

A. Summary of the State of the Art

1. Phenobarbital and Phenobarbital Sodium Were Widely Known and Used

At the time of the alleged invention, phenobarbital and phenobarbital sodium are well-established compounds within the field of pharmaceutical sciences, widely recognized for their anticonvulsant, hypnotic, and sedative effects.

Phenobarbital ($C_{12}H_{12}N_2O_3$) developed by Bayer AG in 1912, was known to be "a typical barbiturate derivative" and was "widely used as a hypnotic, sedative, and seizure treatment for epilepsy in oral, injectable, and suppository formulations." Deliberation Results Report at 3. As of May 30, 2008, oral formulations of phenobarbital were "approved in 22 countries worldwide, including the U.S., the U.K., Germany, and France, and suppositories are approved in one country, Switzerland." *Id.* In Japan, phenobarbital had been "approved in tablets, powders, elixirs, and subcutaneous/intramuscular preparations since the approval of phenobal® powder in January 1944." *Id.*

Phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$), the sodium salt of phenobarbital, was also "approved for subcutaneous/intramuscular use in 1949, and a suppository was approved in March 1980." *Id.* The efficacy and safety of phenobarbital sodium, particularly for status epilepticus, was widely recognized and known to medical and pharmaceutical authorities. *Id.* at 4.

The physical and chemical properties of phenobarbital and phenobarbital sodium were also well-documented at the time of the invention. *E.g.*, West-Ward. According to the Japanese Pharmacopoeia, phenobarbital "occurs as white crystals or crystalline powder" and is "very slightly soluble in water." Japanese Pharmacopoeia at 1389; *see also* Deliberation Results Report at 5. Similarly, the United States Pharmacopeia describes phenobarbital as "[w]hite, odorless,

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glistening, small crystals, or white, crystalline powder" and notes that it is "very slightly soluble in water." USP at 2493; *see also* USP at 5663. This limited solubility in water means that phenobarbital does not readily dissolve, which reduces the rate of degradation in aqueous environments. *See* Deliberation Results Report at 5.

In contrast, phenobarbital sodium, which appears as "flaky crystals, or white, crystalline granules, or white powder," is "very soluble in water." USP at 2493; *see also* USP at 5665-66; West-Ward at § 9. This high solubility means that phenobarbital sodium dissolves readily, which can increase the rate of degradation in aqueous solutions. Phenobarbital sodium is also described as a "white crystal or crystalline powder that . . . is hygroscopic" and "has two types of crystalline forms," which "change by hygroscopic absorption at a relative humidity of 68% or higher." Deliberation Results Report at 4; *see also* USP at 2493 (noting that phenobarbital sodium is "hygroscopic" and its solutions "decompose on standing"). Furthermore, the pH of phenobarbital sodium in water was reported to be between 9.2 and 10.2. USP at 5665; *see also* Nobelbar Label.

Given the extensive prior art and well-documented properties of phenobarbital and phenobarbital sodium, including their solubility characteristics and stability profiles, developing stable pharmaceutical formulations—particularly injectable forms—required addressing these solubility and degradation issues. Specifically, the hygroscopic nature of phenobarbital sodium, coupled with its high solubility, presented significant challenges in formulation development.

2. Phenobarbital Sodium Was Known to Degrade by Residual Water in the Composition and/or in the Atmosphere

In injectable formulations, the stability of a drug is important due to the potential toxicity of impurities formed during storage. *See* Broadhead at 331, 340-41. Consequently, the development of pharmaceutical formulations has focused on strategies to minimize or eliminate

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impurity formation, particularly during the manufacturing process. Liu at 1-3 (teaching that impurities can arise from various sources, including "synthetic/manufacturing processes, degradation, storage conditions [e.g., oxidation, dehydration], container, excipients, or contamination"); Prabu at 66-67. Anderson 2000 explains that "developing procedures to minimize key impurities in a drug substance is generally straightforward" once the structures of the impurities are known and that there are two basic approaches: "to minimize the formation of an impurity, or to minimize the presence of this impurity in the drug substance." Anderson 2000 at 262; *see also* Alsante at 239 (describing the extensive studies conducted to understand the origin and fate of impurities, which helps in determining significant impurities that need routine monitoring); *see generally* Liu (focusing on the importance of managing impurities in pharmaceutical products, particularly those related to active pharmaceutical ingredients, such as degradation-related impurities and interaction-related impurities, and reviewing international regulatory requirements for managing these impurities); Prabu (discussing the importance of understanding and managing impurities in drug substances and products).

Process chemists and engineers have emphasized the need to control impurities to ensure the safety of active pharmaceutical ingredients (APIs), noting that "[t]he economics of failing to control the physical form and impurities in APIs provide good reasons to monitor operations and scrutinize data." Anderson 2012 at 389. The strategies to control impurities can be summarized by the acronym "ACE" for "Avoid, Control, Expel," which includes methods such as choosing different starting materials or positioning impurities several steps before the final product to provide more opportunities to expel them from the API. Anderson 2012 at 384-85; *see also* Alsante at 237 (discussing the importance of controlling impurities within APIs and drug products during the drug development process and highlighting the significance of rapidly

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predicting and assessing the potential for drug product performance changes, particularly concerning impurity formation and associated safety concerns); Liu at 4 (discussing the importance of conducting impurity determination and forced degradation studies to predict potential impurities, develop analytical methods, and understand storage conditions and stability of drug products); Prabu at 68-69 (emphasizing the importance of isolating, characterizing, and qualifying impurities).

Regulatory guidelines further emphasize the necessity of rigorous impurity control. The EMEA Guideline states that "actual and potential impurities most likely to arise during synthesis, purification, and storage of the new drug substance should be identified." EMEA Guideline at 4. Potential genotoxic impurities should be controlled to as low as reasonably practicable (ALARP principle). *Id.* Similarly, the ICH Q3A(R2) and ICH Q3B(R2) provide guidance on impurity content and qualification in new drug substances and drug products, stressing the importance of summarizing and addressing impurities formed during synthesis, purification, and storage. ICH Q3A(R2) at § 3; ICH Q3B(R2) at § 2; Liu at 4 (noting that ICH Q3A(R2) requires that any impurity present in an API at a level greater than the identification threshold must undergo studies to characterize its structure); *id.* at 5 (summarizing five major steps required by ICH Q3B(R2) for controlling these impurities).

Phenobarbital sodium was known to degrade through various pathways, particularly in the presence of water, resulting in the formation of toxic impurities. Particularly, phenobarbital sodium was widely known to be highly susceptible to degradation due to their hygroscopic nature and high solubility in water. *See, e.g.*, Deliberation Results Report at 4; USP at 2493; West-Ward at § 9; *see also* Alsante at 243; Broadhead at 340 (identifying hydrolysis as the "most common mechanism of instability in parenteral formulations"). The presence of hydroxyl ions

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from water in the formulation "results in a hydrolysis pathway that can destroy the phenobarbital ring complex," leading to the formation of "harmful" degradation products such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). Parker at [0004], [0006], [0007], Table 1; *see also* Tishler at Abstract, 214 (disclosing PEAU as a degradant of phenobarbital). These degradation processes are exacerbated by conditions such as reactions with bases, oxidation, and exposure to heat. Parker at [0007].

To address these issues, Parker provides extremely stable phenobarbital sodium solutions for injection that do not generate significant amounts of impurities during extended storage *See id.* at Abstract, [0017]. Parker's formulations include phenobarbital sodium in amounts of 15 to 200 mg/mL, combined with a C1-C4 alcohol, such as ethanol, and a glycol, with a pH between 9 and 12, preferably from 9.2 to 10.2. *Id.* at Abstract, [0017], [0034], [0036], [0039], cls. 1-4. Parker further discloses a container with about 0.5 to about 20 mL of the phenobarbital sodium solutions. *Id.* at [0058], cl. 10. For example, a 0.5 mL vial of phenobarbital sodium at a concentration of 130 mg/mL would provide a 65 mg dose. These solutions contain no more than 50 mg/mL water, significantly reducing the formation of impurities. *Id.* at Abstract, [0017]. The enhanced stability of these solutions is evidenced by containing no more than 0.8% PEAU impurity after two years of storage at room temperature, and no detectable amount of phenyl butyric acid (PBA) impurity after the same period. *Id.* at [0017], cls 1, 6.

The degradation of phenobarbital sodium into impurities such as PEAU, 2EPMM, and PBG is well-documented, with residual water in the composition and/or atmosphere being a primary cause. *See, e.g., id.* at [0004], [0006], [0007], Table 1. Process chemists and engineers aim to control impurities by minimizing the presence of water and other reactive substances.

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These strategies are important to ensuring the stability and safety of phenobarbital sodium formulations, particularly for injectable forms where purity is paramount.

3. Lyophilization of Pharmaceutical Products Has Long Been Well Known and Extensively Utilized in the Industry

Lyophilization, also known as freeze-drying, is a dehydration process widely utilized in the pharmaceutical industry to remove water from products. *See, e.g.*, Broadhead at 340. It is a technique "for the preparation of dry powders to be reconstituted at the time of administration." Brittain 1999 at 213. The process works by freezing the material, reducing the surrounding pressure to allow the ice to change directly from solid to vapor without passing through a liquid phase (primary drying or sublimation), and finally gradually increasing the temperature to remove unfrozen water molecules, reducing the bound water to a minimum (secondary drying or desorption). *See, e.g.*, Brittain 1999 at 214-15; Przic at 552-54; Kern at 2, 19; Sandhyarani at Abstract; FDA_7/93; Broadhead at 340; *see generally* Rey.

The first step in lyophilization is freezing the product. During this stage, the temperature is lowered significantly, typically to -40°C or below, well below the eutectic point, which causes the water in the product to form ice crystals. *See* Pikal at 1807-08; Kern at 21-22; Brittain '190 at 17:63-18:09; FDA_7/93; Broadhead at 340; Rey at 2, 54 (noting that the shelf temperature can drop to -50°C). The initial freezing stage occurs upon cooling aqueous solutions to temperatures below 0°C and "takes place via ice nucleation." Craig at 199. And as the temperature decreases, "molecular mobility decreases and the lifetimes of the [water] aggregates increase, leading to nucleation and subsequent crystal growth." *Id.* The formation of ice crystals separates the solutes and solvents, which helps in minimizing thermal degradation and immobilizes the components to prevent their concentration during drying. Przic at 554. The freezing step is generally done at atmospheric pressure, without application of vacuum. Rey at 16.

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Once the material is completely frozen, primary drying begins. During this stage, the pressure in the freeze-dryer is reduced by placing the frozen material under vacuum, and heat is applied to the product to initiate sublimation of frozen water or the vaporization of another solvent. *See, e.g.*, Brittain 1999 at 215; Craig at 200; Przic at 555 ("Once the formulation has reached a completely frozen state, the pressure in the freeze-dryer is reduced, and heat is applied to the formulation to initiate sublimation of the ice crystals. The application of vacuum allows the free migration of water vapors from the frozen mass."); Rey at 3 ("The sublimation phase or primary drying will follow when the frozen material, placed under vacuum, is progressively heated to deliver enough energy for the ice to sublimate."); *id.* at 16. Sublimation involves converting ice directly into vapor without passing through the liquid phase. Kern at 19. During this phase, it is important to maintain a vacuum of approximately 80 µHg ± 20 µHg (80 mTorr ± 20 mTorr) to prevent product melting. Trappler at Tables 1-2, 5; Przic at 555; *see also* Brittain '190 at 18:10-27. The product temperature should be carefully controlled to avoid heat-induced degradation. Although "[v]arious products require different drying temperatures," drug products typically dry well at temperatures between -5°C. to -32°C. Kern at 23. Primary drying times can vary significantly, often ranging from 48 hours to even several weeks, depending on the product and process design. Pikal at 1807; Przic at Table 3.

After the primary drying phase, secondary drying commences. This phase removes any remaining unfrozen water molecules (or residual solvent) through desorption by gradually increasing the product temperature while maintaining low pressure. Brittain 1999 at 215; Przic at 555-56. The objective is to reduce the moisture content to very low levels, typically less than 2%, to ensure product stability. Przic at 556; Kern at 23 ("[M]oisture is removed from the final dry solid leaving less than 0.5 per cent moisture in the finished product."); Broadhead at 340; *see*

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also Pikal at 1807; Rey at 3 ("For each product an appropriate residual moisture has to be reached under given temperatures and pressures."); *id.* at 242 ("Lyophilization is a process to remove water so that the water activity, or the mobility of the water, in the dried product can be reduced to an optimal level. This is achieved by using a secondary drying cycle."); *id.* at 451. The process involves maintaining the vacuum within the similar range (80 mTorr ± 20 mTorr) while gradually increasing the temperature of the product, usually to 25–60°C, to facilitate the removal of the remaining water. Trappler at Tables 1-2, 5; Craig at 201; Pikal at 1807; Broadhead at 340; *see also* Rey at 16, 451. The secondary drying stage typically takes several hours and can extend up to 24 hours to ensure thorough desorption. Pikal at 1807; Przic at Table 3. This step is important to achieve the desired stability of the lyophilized product. Przic at 556.

The choice of containers and equipment is important to the overall efficiency and effectiveness of the lyophilization process. Pharmaceutical solutions are typically dispensed into glass vials or ampoules. Przic at 553-54. These containers are loaded onto temperature-controlled shelves within a freeze-drying chamber, connected to a condenser chamber that houses plates or coils capable of being maintained at very low temperatures. Pikal at 1807. The design and material of the containers influence heat transfer and vapor flow, impacting the overall drying process. Przic at 553; *see also* Rey at 396-424. Advanced vacuum technologies are employed to create the necessary conditions for sublimation, further ensuring that the product maintains its stability and purity throughout the lyophilization process. Przic at 552.

Lyophilization is especially advantageous for pharmaceutical products because it allows for easy reconstitution at the time of administration. Brittain 1999 at 213. This process has been extensively utilized in the industry, particularly for products intended for parenteral administration. Przic at 552 ("With advances in vacuum technologies reliable commercial freeze-

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dryers were able to be developed. Since that time the method has become fully integrated within the pharmaceutical industry."); *id.* at 557 ("The most extensive use of the lyophilization process is involved in the healthcare industry. This includes the lyophilization of pharmaceuticals such as chemical compounds, parenteral formulations, vaccines, and also in diagnostic products."); *id.* at 559 ("There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products."); *id.* at Table 1; Craig at 198; Pikal at 1807-08; Sandhyarani at Abstract, 51-52; Kern at 2; Brittain '190 at Abstract; Broadhead at 340.

Moreover, many pharmaceuticals can exist in a total or partially amorphous state. Craig at Abstract. "[A]morphous solids consist of disordered arrangements of molecules and therefore possess no distinguishable crystal lattice nor unit cell and consequently have zero crystallinity." Brittain 1999 at 8; *see also* Einfalt at 305 (characterizing amorphous solids by a short-range molecular arrangement similar to crystals but lack long-range order); Yu at 27, 30.

Unlike crystalline materials, amorphous materials are "generally more energetic" and "tend to have higher solubilities and rates of dissolution." Bernstein at 253; *see also* Haleblian at 1273-74; Einfalt at 305, 307; Yu at 27. Thus, "increasing attention is being paid towards the preparation, detection, characterization, and stabilization of amorphous forms." Bernstein at 253. Techniques such as differential scanning calorimetry and X-ray diffraction are used to analyze the physical structures of these drugs. Craig at 179; Yu at 31. Lyophilization can significantly alter the physical forms and dissolution characteristics of pharmaceutical compositions. "The physical form, chemical stability, and dissolution characteristics of lyophilized products can be influenced by the conditions of the freeze-drying cycle." Brittain 1999 at 214. Specifically, lyophilization can be employed to convert crystalline materials to amorphous forms. *Id.*;

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Bernstein at 254 ("Amorphous pharmaceutical materials are typically obtained by employing crystallization procedures far from equilibrium such as . . . lyophilization (free drying) . . . ."); Craig at 180 ("[P]rocesses such as freeze and spray drying may lead to the generation of amorphous systems. . . . [T]he drug, excipient or delivery system may be deliberately produced in an amorphous form in order to enhance product performance characteristics. Examples of this strategy include the preparation of glassy drugs for enhanced dissolution behaviour or freeze drying . . . ."); Einfalt at 308-309 (disclosing lyophilization as a common technique for producing amorphous or partially amorphous systems in pharmaceutical applications); Yu at Abstract, 29 (nothing that amorphous solids are often produced through methods like freeze-drying, with rapid freezing favoring amorphous formation, while annealing may lead to crystallization).

Therefore, to prepare amorphous materials, "rapid freezing is employed so as to avoid the crystallization process." Brittain 1999 at 215. Numerous amorphous pharmaceuticals obtained by lyophilization, including both aqueous solutions and solutions containing organic solvents, have been extensively explored and studied in the literature, such as lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7; *see also* Haleblian at 1272 (noting lyophilization of fluprednisolone in *tert*-butanol to prepare amorphous solids).

Lyophilization is particularly useful for compounds susceptible to decomposition by water, as it reduces water-based degradation. Brittain 1999 at 213-14 ("It is a particularly useful technique in the case of compounds that are susceptible to decomposition in the presence of moisture but that are more stable as dry solids."); Pikal at 1808 ("[A]s the vials are sealed in the freeze dryer, moisture control and control of headspace gas can easily be controlled, an important advantage for products whose storage stability is adversely affected by residual moisture and/or

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oxygen."); Kern at 107 ("Freeze drying seems to reduce the wetability of phenobarbital."); Rey at 82 ("The real benefit of drying is seen long-term, during storage, due to the removal of water, which facilitates many chemical degradation processes, as well as immobilization of the molecule.").

Apart from reducing water-based degradation, lyophilization offers other advantages, making it a versatile and highly effective technique that addresses the challenges of drug stability, sterility, and bioavailability, making it a cornerstone in the production of modern pharmaceutical products, particularly those intended for parenteral administration. *See, e.g.*, Broadhead at 340. One of the primary benefits is the enhanced stability of the dry powder form, which significantly prolongs the shelf life of labile substances by preventing degradation through moisture. Przic at 553 ("The water content of the dried product can be reduced to very low levels. In general the lower the water content the more stable the product . . . ."); Craig at 198 ("The process has found considerable application in the processing of pharmaceutical products of biological origin such as serums, vaccines, peptide drugs and liposomes, as the stability of freeze-dried solids is usually much higher than the equivalent aqueous solution or suspension."); Pikal at 1807 ("Freeze drying, also termed 'lyophilization,' is a drying process employed to convert solutions of labile materials into solids of sufficient stability for distribution and storage."); FDA_7/93; Kern at 4. By removing water without excessive heating, lyophilization preserves the structural integrity and biological activity. FDA_7/93. This method is particularly advantageous for products susceptible to thermal degradation, as freeze-drying is less likely to cause such damage compared to high-temperature processes like spray drying. Pikal at 1808.

Additionally, lyophilization facilitates the rapid and easy reconstitution of the product at the time of administration, which is important for maintaining the efficacy and safety of

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pharmaceuticals. Brittain 1999 at 213; FDA_7/93; Kern at 4. The process also ensures that the product remains free from microbial contamination, as the solution is sterile-filtered before being placed in the final container, and further processing minimizes exposure to contaminants much more effectively than other processes, such as dry powder filling of spray-dried or bulk-crystallized powder. Pikal at 1808.

Furthermore, the reduction of water-based degradation is a significant advantage, particularly for compounds that are more stable as dry solids. *See* Rey at 82; *see also see also* Alsante at 243; Broadhead at 340. Lyophilization reduces oxidative denaturation by sealing the product under vacuum or inert gas, thereby enhancing the overall stability of the product. Przic at 553; Pikal at 1808.

The method also allows for the production of amorphous pharmaceuticals, which can improve the dissolution rate and bioavailability of certain drugs. *See* Haleblian at 1273-74 (finding that the enhanced solubility of amorphous compounds can greatly improve drug absorption compared to their crystalline counterparts); Einfalt at 305, 307; Yu at 27. Rapid freezing during the lyophilization process prevents the formation of crystalline structures, resulting in amorphous products that dissolve more readily. *See* Bernstein at 253. This characteristic is particularly beneficial for drugs that require enhanced dissolution behavior to achieve therapeutic efficacy. Craig at 180.

4. The Lyophilization of Phenobarbital and Phenobarbital Sodium Has Been Well Established, and No Clear Changes Have Been Observed in Stability Studies

The lyophilization of phenobarbital and phenobarbital sodium has been well established and extensively studied as model drugs for lyophilized tablets. Phenobarbital has been a known subject of lyophilization studies to create stable formulations that can be reconstituted at the time

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of administration. Kern at 81. These studies highlighted that phenobarbital and its sodium salt as model drugs for lyophilized tablets demonstrated better mechanical strength compared to those prepared with water-insoluble phenobarbital in its acid form. Sznitowska at Abstract. These studies further noted that incorporating phenobarbital sodium at higher doses reduced the tablets' plasticity and porosity. *Id.*

Lyophilized phenobarbital sodium has also been available on the market at the time of the alleged invention. A notable example is Nobelbar, Japan's first phenobarbital drug for intravenous injection. As the efficacy and safety of the drug have been demonstrated, Nobelbar 250 mg for injection has been marketed since December 2008 in Japan. Kawada 2011 at 210; Deliberation Results Report at 2. This lyophilized product contains 274 mg of phenobarbital sodium per vial (equivalent to 250 mg of phenobarbital) and is used for neonatal convulsions and status epilepticus. Deliberation Results Report at 1. The approved dosage of Nobelbar for neonatal convulsions is an initial dose of 20 mg/kg intravenously, with additional doses administered as needed, not exceeding the initial dose, and a maintenance dose of 2.5 to 5 mg/kg intravenously once daily. *Id.* at 2. For status epilepticus, the approved dosage is 15 to 20 mg/kg intravenously once daily. *Id.* Nobelbar is "a lyophilized injection composed of drug substance only, without additives, with a clear colorless glass vial/rubber stopper/flip cap applied to the container and closure system." *Id.* at 5; *see also* Kawada 2011 at 205 ("A lyophilized product of phenobarbital sodium entirely free of additives was used in this study."). Unlike other phenobarbital sodium products, which contain organic solvents, Nobelbar addressed a strong demand for the development of a phenobarbital preparation that is free of additives. Kawada 2011 at 205-06 ("[D]ue to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic solvents such as benzyl alcohol and

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propylene glycol, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives."); *see also* Kawada 2009 at 660-01 ("[W]hen possible, it is preferable to use a drug product that does not contain these additives especially in newborns and low birth weight infants. . . . [E]arly development of intravenous preparations containing no additives in Japan has been strongly desired by academic societies."). Moreover, "there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the drug." Kawada 2011 at 209-10. Nobelbar is also easily dissolved in water and decomposes by approximately 6% within 24 hours after dissolution. Kawada 2009 at 657.

Stability studies of Nobelbar have shown "no clear changes" in the drug substance's and drug formulation's properties over extensive testing periods, including long-term storage tests (25 ± 2°C/60 ± 5% RH, in a dark location, 60 months) and accelerated tests (40 ± 2°C/75 ± 5% RH, dark place, 6 months). Deliberation Results Report at 5. These tests covered various parameters such as solubility, pH, purity, moisture, and microbial limits, with no clear changes observed, confirming the stability of the lyophilized product. *Id.* Nobelbar was also reported to have a shelf life of 3 or 4 years. Deliberation Results Report at 5.

Another example of a well-established lyophilized phenobarbital sodium product on market is Gardenal, which is used for subcutaneous or intramuscular injections. *See* Bertaux at 656; Fournier at 1584. Gardenal is dissolved in sterile normal saline and administered to rats in various studies to evaluate its effect. Bertaux at 656; Fournier at 1584. This further exemplifies

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the long-standing application of lyophilization in producing stable phenobarbital sodium products. Gardenal was also reported to have a shelf life of 3 years. Gardenal Label.[8]

The stability of APIs and finished pharmaceutical products is important for ensuring their efficacy and safety over time. Stability testing is conducted under standardized conditions, including specific temperature, relative humidity, and time parameters, to provide reliable data on the product's shelf life and to establish degradation pathways in order to identify the likely degradation products. *See* EMEA ICH Topic Q1A at 1, 3; FDA Guidance for Industry Q1A(R2) at 2 ("The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions."); *id.* at 3 (emphasizing the importance of stress testing, which helps identify likely degradation products, establish degradation pathways, and validate the stability-indicating power of analytical procedures).

For long-term stability studies of an API, the general storage conditions are 25 °C ± 2 °C/60% RH ± 5% RH, 30 °C ± 2 °C/65% RH ± 5% RH, or 30 °C ± 2 °C/75% RH ± 5% RH for 12 months or 6 months. Annex 10 at Table 2.1.7.1; *see also* EMEA ICH Topic Q1A at 3; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14. Intermediate studies of an API typically use storage conditions of 30 °C ± 2 °C/65% RH ± 5% RH for 6 months, while accelerated studies are generally conducted at 40 °C ± 2 °C/75% RH ± 5% RH for 6 months. Annex 10 at Table 2.1.7.1; *see also* EMEA ICH Topic Q1A at 3; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14. For

[8] Gardenal Label was published in July 2014 and is therefore prior art to the Patents-in-Suit under 35 U.S.C. § 102.

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APIs intended for storage in a refrigerator, the long-term study condition is 5 °C ± 3 °C for 12 months or 6 months, with the accelerated study conditions being the same as those for long-term storage of non-refrigerated APIs. Annex 10 at Table 2.1.7.2. For finished pharmaceutical products, the long-term storage conditions are similar: 25 °C ± 2 °C/60% RH ± 5% RH, 30 °C ± 2 °C/65% RH ± 5% RH, or 30 °C ± 2 °C/75% RH ± 5% RH for 12 months or 6 months, with intermediate studies at 30 °C ± 2 °C/65% RH ± 5% RH for 6 months, and accelerated studies at 40 °C ± 2 °C/75% RH ± 5% RH for 6 months. Annex 10 at Table 2.2.7.1; *see also* EMEA ICH Topic Q1A at 6; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14.

These standardized conditions ensure that the product maintains its intended quality throughout its shelf life. Annex 10 at 313, 315, 321-322, 324-45; *see also* EMEA ICH Topic Q1A at 3-4, 7-8; FDA Guidance for Industry Q1A(R2) at 2. Stability after reconstitution or dilution must be evaluated under these standardized conditions to provide comprehensive data supporting labeling and storage instructions. EMEA ICH Topic Q1A at 6-8.

For lyophilized products, stability testing also includes the analysis of aged samples and subsequent reconstitution. The FDA's guidelines emphasize the importance of having data that demonstrates adequate stability at specified moisture limits and conducting stability testing that includes provisions for the assay of aged samples for the maximum amount of time specified in the labeling. FDA_7/93.

Consequently, the lyophilization of phenobarbital sodium has been well established in the pharmaceutical industry, with numerous studies demonstrating the stability and efficacy of lyophilized phenobarbital sodium products. Stability studies conducted under standardized conditions have shown no significant changes in the product's properties, suggesting that

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lyophilization is an effective method for producing stable phenobarbital sodium formulations that maintain their quality over time with no significant amount of impurities.

5. 65 mg and 130 mg Dosages of Phenobarbital Sodium Were Also Known

Phenobarbital sodium injection has been available in concentrations of 65 mg/mL and 130 mg/mL, providing precise and effective dosage forms. For example, Hikma Pharmaceuticals has produced phenobarbital sodium injection in these concentrations, with a fill volume of 1 mL. Hikma at 35 and 62. The availability of these specific dosages ensures that healthcare providers can administer appropriate therapeutic levels of phenobarbital to patients in various clinical scenarios. Moreover, pursuant to the Deliberation Results Report, the loading dose of phenobarbital sodium is 20 mg/kg. Deliberation Results Report at 2. A POSA would have understood that a vial containing 65 mg of phenobarbital sodium would translate to a single use dose for a neonate having a body weight of 3.25 kg (or roughly 7 pounds) and that a vial containing 130 mg of phenobarbital sodium would translate to a single use dose for an infant having a body weight of about 6.5 kg (or roughly 14 pounds).

These vials are typically single use, ensuring that each dose is sterile and accurately measured. Typically, medication intended for parenteral administration is typically packaged in single-dose vials. Silberzweig at 111. Single use vials are important in medical settings as they minimize the risk of contamination and ensure patient safety by preventing dosage errors. Single dose vials, unlike multi-dose packaging, allow each dose to be sealed and used individually, reducing the risk of contamination. *See* Silberzweig at 111 ("The preservative agents [found in multiple-dose vials] has no effect on viruses and does not protect against contamination when healthcare personnel fail to follow safe injection practices."); Bawden at 294-97 (finding that multiple-dose vials for intravenous or intramuscular use are a significant potential source of

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infection); Mattner at Abstract, 12-14 (highlighting the "somewhat risky handling" practices of multiple-use vials). Additionally, they simplify monitoring of patient medication intake, helping prevent overdoses and ensuring accurate record-keeping. Single-dose packaging also reduces waste, as patients receive only the doses they need, and any unused medication can be safely allocated to other patients without cross-contamination concerns. The practice of using single-use vials aligns with standard medical protocols to maintain sterility and efficacy in injectable medications.

6. Sparging Water With Nitrogen Was a Commonly Used Technique

Sparging water with nitrogen is a well-established technique for removing dissolved oxygen, which is important when working with redox-sensitive reagents. It is also important to effectively eliminate dissolved oxygen from solutions as the presence of dissolved oxygen in water can lead to unwanted oxidation reactions that may compromise the integrity and stability of sensitive chemical processes. Butler at 211.

There are both chemical and physical methods available for removing dissolved oxygen from water. Among these, chemical methods have proven particularly effective. *See generally* Butler. One of the most effective techniques is nitrogen gas purging. *Id.* at Abstract, 213. In this method, nitrogen gas is bubbled into the water for 20-40 minutes at a flow rate of 25 mL/s. *Id.* at Abstract, 211. This process significantly reduces the concentration of residual dissolved oxygen, typically bringing it down to about 0.2 to 0.4 ppm after purging for the specified duration. *Id.* at Abstract. The efficiency of nitrogen purging is enhanced by using pre-purified grade nitrogen, a sintered glass bubbler, high gas flow rates, and an airtight container with a small vent hole to allow the purge gas to escape. *Id.* at 214.

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One of the advantages of nitrogen purging over other methods is that it maintains the solution at a cool temperature, making it immediately ready for use after the oxygen removal process. *Id.* at 214. This is in contrast to methods like boiling, which require additional time for the solution to cool down before it can be used. *Id.*

However, a potential drawback of nitrogen purging is that nitrogen itself remains dissolved in the solution after the oxygen is purged. *Id.* at 214. While this does not typically interfere with most applications, it is a consideration that must be taken into account in processes where the presence of dissolved nitrogen might affect the outcome.

Overall, the practice of sparging water with nitrogen is a widely recognized and effective technique in the field of pharmaceutical sciences, providing a reliable means to prepare oxygen-free water necessary for various sensitive applications.

B. The Claims of the ’598 and ’076 Patent are Obvious

1. The Claims of the ’598 Patent Are Obvious in View of the Prior Art

Sun contends that the references described in Sections VI and VII.A above, along with the common knowledge in the art at least as of September 20, 2019[9], render all of the claims of the ’598 Patent obvious under 35 U.S.C. § 103.

In general, Sun contends that the motivation or reason to combine or modify prior art to create invalidating combinations under 35 U.S.C. § 103 can be found in the references identified above in Sections VI and VII.A. To the extent that any limitation is not explicitly disclosed in a prior art reference discussed above, it would have been achieved through routine optimization by one of ordinary skill in the art. *See, e.g.*, *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980). For at

[9] On its face, the ’598 Patent identifies the ’511 application, filed on September 20, 2019, as a related application. *See supra* Section III.A. Furthermore, the common knowledge in the art would also support the invalidity of all of the claims of the Patents-in-Suit even if Plaintiff successfully asserts an earlier priority date.

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least these additional reasons, any such limitation would have been rendered obvious as well. *See also KSR*, 550 U.S. at 416-17. Common sense, design incentives, market forces, and the background knowledge possessed by a POSA provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the subject matter of the claims of the ’598 Patent.

a. Obviousness of Independent Claim 1

The state of the art from Section VII.A is incorporated herein, as is the scope and content of the prior art from Section VI. Sun also presents the following analysis specific to claim 1 of the ’598 Patent.

Independent claim 1 of the ’598 Patent is directed to a method of producing a storage-stable form of lyophilized amorphous phenobarbital sodium composition, comprising adding phenobarbital sodium to water to form a solution with a pH between 9.2 and 10.2, ensuring the solution does not contain organic solvents, and optionally, including sodium chloride. ’598 Patent at cl. 1. The claim also includes various lyophilization parameters and steps to achieve a lyophilized composition with an initial moisture content of 1.5% or less, and upon reconstitution in an aqueous solution after three months of storage, the lyophilized composition forms no more than 0.2% phenylethylacetylurea (PEAU). *Id.*

A POSA would have been motivated and would have had a reasonable expectation of success in producing the claimed storage-stable form of lyophilized amorphous phenobarbital sodium composition.

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i. A POSA Would Have Known that Lyophilized Phenobarbital Sodium Drug Products Were Tested as Model Drugs and Already on the Market and Would Have Been Motivated and Would Have Had a Reasonable Expectation of Success in Producing a Storage-Stable Form of Lyophilized Phenobarbital Sodium Composition Wherein the Phenobarbital Sodium Solution Has a pH of Between 9.2 and 10.2 and Does Not Contain an Organic Solvent

At the time of the alleged invention, a POSA would have been well aware of the widespread use and established properties of phenobarbital sodium. *See supra* Section VII.A.1. Phenobarbital sodium, the sodium salt of phenobarbital, had been approved for subcutaneous and intramuscular use since 1949, and was recognized for its anticonvulsant, hypnotic, and sedative effects. Deliberation Results Report at 3. The physical and chemical properties of phenobarbital sodium, including its solubility and stability characteristics, were well-documented. *See* USP at 2493, 5665-66; West-Ward at § 9; Deliberation Results Report at 4. Furthermore, the pH of phenobarbital sodium in water was reported to be between 9.2 and 10.2. USP at 5665; *see also* Nobelbar Label. This extensive prior art would have provided important information for developing stable pharmaceutical formulations.

The lyophilization of phenobarbital sodium had been extensively studied to create stable formulations. Studies demonstrated that lyophilized phenobarbital sodium served as a model drug for lyophilized tablets, showing better mechanical strength and reduced plasticity and porosity at higher doses. Kern at 81; Sznitowska at Abstract. Additionally, lyophilized phenobarbital sodium products like Nobelbar had been marketed, proving the efficacy and safety of such formulations. *See, e.g.*, Kawada 2011 at 210; Deliberation Results Report at 2. Nobelbar, Japan's first phenobarbital drug for intravenous injection, addressed the demand for a phenobarbital preparation free of additives and demonstrated stability over extensive testing

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periods. Kawada 2011 at 205-06; Kawada 2009 at 660-01; Deliberation Results Report at 5. Unlike other phenobarbital sodium products, which contain organic solvents, Nobelbar was free of such additives, meeting a need for phenobarbital preparations for neonatal and pediatric use. Kawada 2011 at 205-06; Kawada 2009 at 660-01.

A POSA would understand the significance of Nobelbar's formulation, which excludes organic solvents, due to the documented instability of phenobarbital sodium in water and the potential concerns of organic solvents in pediatric and neonatal applications. *See supra* Section VII.A.2. Nobelbar's success in the market highlighted the feasibility and advantages of producing a lyophilized phenobarbital sodium composition free of organic solvents, thus motivating further development in this direction. *See* Kawada 2011 at 205-06; Kawada 2009 at 660-01.

Moreover, other phenobarbital sodium solutions, such as Parker's formulations, provided extremely stable solutions for injection without generating significant amounts of impurities during extended storage. *See generally* Parker. Parker's formulations included phenobarbital sodium in amounts of 15 to 200 mg/mL, with the solution having a pH of between 9 and 12, preferably between 9.2 and 10.2. Parker Abstract, [0017], [0034], [0036], [0039]. A POSA would have recognized that this pH range was appropriate for maintaining the stability and solubility of phenobarbital sodium, ensuring its efficacy over time.

Another example, Gardenal, used for subcutaneous or intramuscular injections, further exemplified the application of lyophilization in producing stable phenobarbital sodium products. Bertaux at 656; Fournier at 1584. Stability studies under standardized conditions confirmed the long-term stability and quality of these products, ensuring their efficacy and safety over time. *See*

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Annex 10 at Tables 2.1.7.1, 2.2.7.1; EMEA ICH Topic Q1A at 3, 6; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14; FDA_7/93.

Given the established knowledge and successful examples, a POSA would have been motivated to develop a lyophilized phenobarbital sodium composition with a pH between 9.2 and 10.2, as this pH range was documented for phenobarbital sodium in water and was proven to be effective in maintaining stability. *See* USP at 5665; *see also* Nobelbar Label. The documented success of formulations like Parker's, which maintained stability without generating significant impurities, would provide a POSA with confidence in achieving similar results in a lyophilized form. *See supra* Section VII.A.2. Furthermore, the absence of organic solvents in Nobelbar demonstrated that it was feasible to produce a stable phenobarbital sodium composition without these additives.

Consequently, the extensive prior art and documented properties of phenobarbital sodium, along with the successful development and market presence of lyophilized phenobarbital sodium products such as Nobelbar and Gardenal, clearly demonstrate that a POSA would have been aware of the viability and effectiveness of lyophilizing phenobarbital sodium. A POSA would have known and would have been motivated, and would have had a reasonable expectation of success in producing a storage-stable form of lyophilized phenobarbital sodium composition wherein the phenobarbital sodium solution has a pH of between 9.2 and 10.2 and does not contain an organic solvent.

ii. A POSA Would Have Recognized that Lyophilization was a Technique Which Was Widely Employed for Pharmaceutical Products and Would Have Been Motivated, with a Reasonable Expectation of Success, to Apply the Claimed Lyophilization Parameters to Phenobarbital Sodium Solution in a Container

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A POSA would have recognized that lyophilization was a widely employed technique in the pharmaceutical industry for producing stable, dry powders from aqueous solutions, typically carried out within a container such as a glass vial or ampoule. *See supra* Section VII.A.3. This technique, also known as freeze-drying, involves three steps: freezing, primary drying, and secondary drying. *See, e.g.*, Brittain 1999 at 214-15; Przic at 552-54; Kern at 2, 19; Sandhyarani at Abstract; FDA_7/93; Broadhead at 340; *see generally* Rey. Each of these steps employs specific parameters of temperature, pressure, and duration to ensure the stability and efficacy of the final product. These steps are well-documented in pharmaceutical literature and are fundamental in the production of many drug products.

The initial step in lyophilization is freezing the product. During this phase, the temperature is lowered significantly, typically to around -40°C or below, causing the water in the product to form ice crystals. *See* Pikal at 1807-08; Kern at 21-22; Brittain ’190 at 17:63-18:09; FDA_7/93; Rey at 2, 54; Broadhead at 340. This stage is important as it separates solutes and solvents, minimizing thermal degradation and immobilizing the components to prevent their concentration during drying. Przic at 554. A POSA would understand that this step is typically performed at atmospheric pressure, without application of vacuum. Rey at 16. This knowledge would motivate a POSA to implement a freezing step at about −50° C. without the application of vacuum, ensuring the product is adequately prepared for the subsequent drying phases.

Once the material is completely frozen, the primary drying phase begins. During this stage, the pressure in the freeze-dryer is reduced under vacuum, and heat is applied to the product to initiate sublimation of the frozen water. *See, e.g.*, Brittain 1999 at 215; Craig at 200; Przic at 555; Rey at 3, 16. Sublimation involves converting ice directly into vapor without passing through the liquid phase, a process facilitated by maintaining a vacuum. Kern at 19;

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Trappler at Tables 1-2, 5; Przic at 555. The primary drying phase typically requires a vacuum of approximately 80 µHg ± 20 µHg (80 mTorr ± 20 mTorr) and a temperature range between -5°C. to -32°C. Kern at 23; Trappler at Tables 1-2, 5; Przic at 555. Maintaining these conditions is important to prevent the product from melting and to ensure efficient sublimation. Primary drying times can vary but often extend to at least 1,000 minutes, from 48 hours to even several weeks, to achieve the desired moisture content in the product. Pikal at 1807; Przic at Table 3.

The secondary drying phase follows primary drying, focusing on removing any remaining unfrozen water molecules through desorption. This phase involves gradually increasing the product temperature while maintaining low pressure to reduce the moisture content to very low levels, typically less than 2%, ensuring product stability. Przic at 556; Kern at 23; Broadhead at 340; *see also* Pikal at 1807. For the secondary drying step, the vacuum is maintained at pressures of approximately 80 µHg ± 20 µHg (80 mTorr ± 20 mTorr), and temperatures are increased to a range of 25°C to 60°C. Trappler at Tables 1-2, 5; Craig at 201; Pikal at 1807; Rey at 16, 451; Broadhead at 340. This step usually lasts at least 200 minutes and can extend up to 24 hours, ensuring thorough removal of residual moisture and achieving the desired stability for the lyophilized product. Pikal at 1807; Przic at Table 3.

As detailed above, the choice of containers and equipment is a consideration to the overall efficiency and effectiveness of the lyophilization process, influencing heat transfer and vapor flow, and ensuring that the product maintains its stability and purity throughout the process. *See supra* Section VII.A.3; *see also* Przic at 553-54; Rey at 396-424.

A POSA would be motivated to employ these specific lyophilization parameters (temperature, pressure, and duration) due to their well-documented effectiveness in achieving stable, dry pharmaceutical products. The extensive use of lyophilization in the pharmaceutical

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industry for products intended for parenteral administration, such as anti-infectives, biotechnology-derived products, and in-vitro diagnostics, demonstrates its reliability and versatility. Przic 552, 557, 559; Broadhead at 340. Moreover, lyophilization's ability to preserve the structural integrity and biological activity of labile substances by removing water without excessive heating further underscores its suitability for producing storage-stable pharmaceutical formulations. Pikal at 1807; FDA_7/93. A POSA would be further motivated to use lyophilization because it can improve the dissolution rate and bioavailability of certain drugs, particularly for drugs that must be reconstituted prior to administration. Craig at 180.

Given the well-established parameters and widespread application of lyophilization in the pharmaceutical industry, a POSA would have a reasonable expectation of success in producing the claimed storage-stable form of lyophilized phenobarbital sodium composition. By employing the known lyophilization process parameters of temperature, pressure, and duration, a POSA would lyophilize the phenobarbital sodium solution in a container under a protocol comprising a freezing step, a primary drying step, and a secondary drying step, which would include (1) freezing the phenobarbital sodium to a temperature of about −50°C without application of vacuum; (2) applying vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about −50°C and about 0°C for a duration of at least 1,000 minutes; and (3) applying vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about 25°C and about 50°C for a duration of at least 200 minutes, to ensure the stability and efficacy of the final product.

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iii. A POSA Would Have Recognized that Lyophilized Phenobarbital Sodium Drug Products Would Have Low Moisture Content and Contain Amorphous Pharmaceutical Compositions

A POSA would have recognized that lyophilization was a common technique to alter the physical form, chemical stability, and dissolution characteristics of pharmaceutical products, making it a preferred method for enhancing the performance of various drugs. Brittain 1999 at 214; *see supra* Section VII.A.3. Specifically, lyophilization is employed to convert crystalline materials to amorphous forms by preventing the formation of crystalline structures during the rapid freezing process. Brittain 1999 at 214-15; Bernstein at 254; Craig at 180; Einfalt at 308-309; Yu at Abstract, 29. The amorphous form of a drug often enhances its dissolution rate and bioavailability, making it a preferred form for certain pharmaceutical applications. Craig at 180; *See* Bernstein at 253; Halebliane; Einfalt at 305, 307; Yu at 27. Furthermore, prior art provides numerous examples of successful applications of lyophilization to produce amorphous pharmaceuticals, including lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7; Haleblian at 1272. A POSA would have known that using the lyophilization parameters as described in Section VII.B.1.a.ii would produce a storage-stable form of lyophilized *amorphous* phenobarbital sodium composition. By following these parameters, including the temperature, pressure, and duration, a POSA would ensure that the lyophilized phenobarbital sodium composition would be in an amorphous state.

Moreover, the purpose of lyophilization was well-known to include the removal of moisture from pharmaceutical products. *See, e.g.*, Brittain 1999 at 214-15. The secondary drying phase of lyophilization specifically aims to reduce the water content to very low levels, ensuring product stability. Prior art teaches that moisture content should be reduced to 2% or less during secondary drying, leaving less than 0.5% moisture in the finished product. Przic at 556; Kern at

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23; Broadhead at 340; *see also* Pikal at 1807; Rey at 3, 242, 451. This low moisture content is important for preventing degradation and maintaining the stability of the lyophilized product.

Therefore, a POSA, equipped with the extensive knowledge from the prior art, would have been motivated and would have had a reasonable expectation of success in using lyophilization to produce the claimed storage-stable form of lyophilized amorphous phenobarbital sodium composition. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms, along with the known methods for achieving initial moisture content of 1.5% or less, would guide a POSA in developing a stable and effective lyophilized phenobarbital sodium composition.

iv. A POSA Would Have Known that Phenobarbital Sodium Can Degrade to Produce Harmful Compounds Such as Phenylethylacetylurea (PEAU), 2-Ethyl-2-phenylmalonamide (2EPMM), and Alpha-phenylbutyrylguanidine (PBG)

A POSA would have recognized that phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation. *See supra* Sections VII.A.1-2. Phenobarbital sodium was known to be "very soluble in water." USP at 2493; *see also* USP at 5665-66; West-Ward at § 9. This high solubility means that phenobarbital sodium dissolves readily, which can increase the rate of degradation in aqueous solutions. Deliberation Results Report at 4; *see also* USP at 2493. The degradation of phenobarbital sodium in the presence of water, bases, oxidation, and heat presents challenges in formulation development, particularly for injectable forms where stability is important. Parker at [0007]; Deliberation Results Report at 4. Phenobarbital sodium's susceptibility to hydrolysis in the presence of hydroxyl ions from water leads to the destruction of the phenobarbital ring complex, resulting in the formation of "harmful" degradation products such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide

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(2EPMM), and alpha-phenylbutyrylguanidine (PBG). Parker at [0004], [0006], [0007], Table 1; *see also* Tishler at Abstract, 214 (disclosing PEAU as a degradant of phenobarbital).

Regulatory guidelines and industry standards emphasize the need to control impurities in pharmaceutical formulations to ensure the safety of APIs. *See supra* Section VII.A.2. For example, the EMEA Guideline, ICH Q3A(R2), and ICH Q3B(R2) stress the importance of identifying and controlling actual and potential impurities that may arise during synthesis, purification, and storage. EMEA Guideline at 4; ICH Q3A(R2) at § 3; ICH Q3B(R2) at § 2. In the context of phenobarbital sodium, the degradation products PEAU, 2EPMM, and PBG are well-documented, highlighting the necessity of stringent impurity control. Parker at [0004], [0006], [0007], Table 1.

To address the issue of degradation, strategies to minimize the presence of impurities include the use of stable formulations that prevent the formation of significant amounts of degradation products during storage. *See* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. Parker, for instance, provides formulations that include phenobarbital sodium combined with a C1-C4 alcohol, such as ethanol, and a glycol, with a pH between 9 and 12, preferably from 9.2 to 10.2. *Id.* at Abstract, [0017], [0034], [0036], [0039], cls. 1-4. These formulations are designed to be extremely stable and do not generate significant amounts of impurities during extended storage. *Id.* at Abstract, [0017].

The presence of impurities such as PEAU, 2EPMM, and PBG, even in minimal amounts, underscores the need for rigorous impurity control in phenobarbital sodium formulations. The prior art demonstrates that maintaining low moisture content is important to minimizing these impurities. *Id.* at Abstract, [0017]. For example, Parker's stable phenobarbital sodium solutions contain no more than 0.8% PEAU impurity after two years of storage at room temperature, and

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no detectable amount of PBG impurity after the same period. *Id.* at [0017], cls. 1, 6. This highlights the importance of formulation strategies that focus on controlling moisture content and other factors that contribute to degradation.

Accordingly, a POSA would have known that phenobarbital sodium can degrade to produce harmful degradants such as PEAU, 2EPMM, and PBG. The well-documented susceptibility of phenobarbital sodium to degradation due to its hygroscopic nature and high solubility in water would have motivated a POSA to employ strategies to control and minimize degradation products, ensuring the stability and safety of the pharmaceutical formulation.

v. A POSA Would Have Recognized that Lyophilized Phenobarbital Sodium Drug Products Would Form No More Than 0.2% PEAU When Reconstituted in an Aqueous Solution Upon Storage over 3 Months

As detailed above in Sections VII.A.2 and VII.B.1.a.iv, a POSA would have recognized that phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in the formation of degradation products such as PEAU. A POSA would have known PEAU as a potential "harmful" degradant of phenobarbital sodium and would be motivated to employ strategies to minimize such impurity when a lyophilized phenobarbital sodium drug product is reconstituted in an aqueous solution. *See* Parker at [0004], [0006], [0007], Table 1.

Stability testing, commonly performed to assess the degradation profile of pharmaceutical products, would be important to this process. *See* supra Sections VII.A.4. Nobelbar, for instance, reported "no clear changes were observed in any of the test items" when the stability of the formulation was evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation

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Results Report at 5. These stability studies confirm the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation.

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar, a POSA would have recognized that lyophilized phenobarbital sodium drug products, using known lyophilization parameters, would form no more than 0.2% PEAU when reconstituted in an aqueous solution upon storage over three months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. The strategies employed to control moisture content and maintain the stability of the drug product would ensure that the formation of harmful degradation products is minimized.

Consequently, based on the prior art and known understanding of common lyophilization techniques, a POSA would have been motivated to pursue, with a reasonable expectation of success, a storage-stable form of lyophilized amorphous phenobarbital sodium composition by adding phenobarbital sodium to water to form a solution with a pH between 9.2 and 10.2, without any organic solvent, and ensuring that the composition has an initial moisture content of 1.5% or less and forms no more than 0.2% PEAU when reconstituted in an aqueous solution after 3 months of storage.

As such, claim 1 of the '598 Patent is obvious over the scope and content of prior art discussed in Sections VI, VII.A, and VII.B.1, in view of common knowledge in the art and the practice of employing common lyophilization techniques.

By way of a non-limiting, illustrative example, claim 1 of the '598 Patent is obvious over one or more of Nobelbar (as evidenced by Deliberation Results Report, Kawada 2009, Kawada 2011, Nobelbar Label, and any other information about Nobelbar gained during discovery),

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Gardenal (as evidenced by Bertaux, Fournier, and any other information about Gardenal gained during discovery), Kern, and/or Sznitowska (collectively, **Group 1 references**) in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references in view of one or more of Parker, Tishler, USP, and/or West-Ward (collectively, **Group 2 references**). It is also obvious over one or more of these references further in view of one or more of Rey, Brittain 1999, Przic, Sandhyarani, FDA_7/93, Pikal, Brittain '190, Craig, Bernstein, Haleblian, Einfalt, Yu, Broadhead, and/or Trappler (collectively, **Group 3 references**). It is also obvious over one or more of these references further in view of one or more of EMEA Guideline, ICH Q3A(R2), ICH Q3B(R2), Anderson 2000, Anderson 2012, Alsante, Liu, and/or Prabu (collectively, **Group 4 references**). A POSA would have been motivated to produce a storage-stable form of amorphous lyophilized phenobarbital sodium composition by adding phenobarbital sodium to water to form a solution with a pH between 9.2 and 10.2, ensuring the solution does not contain organic solvents, based on the lyophilized phenobarbital sodium drug products that were tested as model drugs and already on the market described in the **Group 1 references**. A POSA would have also expected the drug product to have an initial moisture content of 1.5% or less and, upon reconstitution in an aqueous solution after three months of storage, to form no more than 0.2% phenylethylacetylurea (PEAU) for the reasons already discussed in Sections VII.A and VII.B.1.a.i-v. A POSA would have known and thus would have been motivated to reduce PEAU, with a reasonable expectation of success, as a result of their general knowledge. This motivation and reasonable expectation of success would be supported by the ordinary knowledge of a POSA and/or **Group 2 references**. This motivation is further supported by the **Group 4 references**. A POSA would have also known and thus would have been motivated to employ common lyophilization techniques, with a reasonable expectation of

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success, as a result of their general knowledge. This motivation and reasonable expectation of success are supported by the disclosures of the **Group 3 references**.

b. Obviousness of the Dependent Claims

The state of the art from Section VII.A, the scope and content of the prior art from Section VI, and the analyses presented for claim 1 from Section VII.B.1.a are incorporated herein. Sun also presents the following analysis specific to the dependent claims of the '598 Patent.

Claim 2 of the '598 Patent depends from claim 1 and further requires that sodium chloride be present in the phenobarbital sodium solution in an amount that, upon reconstitution of the lyophilized amorphous phenobarbital sodium in the aqueous solution, yields a sodium chloride concentration of 0.9% in the reconstituted solution. '598 Patent at cl. 2. A POSA would have known and been motivated, with a reasonable expectation of success, that lyophilized phenobarbital sodium can be reconstituted in an aqueous solution, specifically in a saline solution. The Nobelbar Label discloses that Nobelbar should be dissolved in physiological saline. *See* Nobelbar Label. Bertaux also demonstrates that lyophilized sodium phenobarbital, such as Gardenal for subcutaneous or intramuscular injection, was successfully dissolved in "apyrogenic sterile normal saline" and administered subcutaneously. Bertaux at 656. Additionally, Broadhead discloses that parenterals can be added to 0.9% sodium chloride infusion/injection for administration. Broadhead at 332. The practice of reconstituting lyophilized products in 0.9% sodium chloride is also well-established in the field, as evidenced by Sandhyarani, wherein lyophilized apo-acetazolamide was reconstituted using 0.9% sodium chloride injection. Sandhyarani at 59. Furthermore, Brittain '190 teaches that lyophilized bendamustine, another pharmaceutical formulation, can be reconstituted and diluted into 500 mL of 0.9% sodium

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chloride for injection, underscoring the general applicability of this approach to various lyophilized products. Brittain ’190 at 2:9-11. Therefore, a POSA would reasonably expect that lyophilized phenobarbital sodium can be effectively reconstituted in an aqueous solution to achieve a sodium chloride concentration of 0.9% in the reconstituted solution. Therefore, claim 2 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 3 of the ’598 Patent depends from claim 1 and further requires that the phenobarbital sodium solution in the container is present in an amount of about 65 mg, or about 100 mg, or about 130 mg, or about 200 mg. ’598 Patent at cl. 3. As discussed above in Section VII.A.5, these specific dosages are well-documented in the pharmaceutical industry. A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg based on the prior art. Phenobarbital sodium injection has been available in concentrations of 65 mg/mL and 130 mg/mL with a fill volume of 1 mL, providing precise and effective dosage forms. Hikma at 35 and 62. A POSA would have recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg is both feasible and supported by existing clinical use.

Moreover, a POSA would have been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights. Understanding the need for tailored dosing, a POSA would recognize

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that different concentrations of phenobarbital sodium solutions, such as 65 mg and 130 mg, would allow for precise dosing based on a patient's weight. Parker describes phenobarbital sodium solutions for injection "in an amount of 15 to 200 mg/mL." Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 65 mg of phenobarbital sodium would be suitable for a neonate with a body weight of about 3.25 kg (approximately 7 pounds), while a vial containing 130 mg would be appropriate for an infant weighing about 6.5 kg (around 14 pounds). Thus, claim 3 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a, optionally further in view of Hikma.

Claim 4 of the '598 Patent depends from claim 1 and further requires that the water is sparged with nitrogen. '598 Patent at cl. 4. As discussed above in Sections VII.A.2 and VII.B.1.a.iv, sodium phenobarbital was known to degrade through various pathways, particularly in the presence of water, resulting in the formation of toxic impurities, and the degradation processes are exacerbated by conditions such as reactions with bases, oxidation, and exposure to heat. Moreover, as discussed above in Section VII.A.6, sparging water with nitrogen is a well-established technique in the field of pharmaceutical sciences for removing dissolved oxygen, which is important when working with redox-sensitive reagents. The presence of dissolved oxygen in water can lead to unwanted oxidation reactions that may compromise the integrity and stability of sensitive chemical processes. Butler at 211.

Given the susceptibility of phenobarbital sodium to degradation in the presence of water and the established efficacy of nitrogen sparging in removing dissolved oxygen, a POSA would

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have been motivated to employ this technique. The prior art clearly demonstrates that nitrogen sparging is an effective method for reducing dissolved oxygen levels and thereby minimizing oxidation and other degradation processes. This motivation, combined with the known susceptibility of phenobarbital sodium to hydrolysis and oxidation, would have provided a POSA with a reasonable expectation of success in using nitrogen-sparged water to stabilize phenobarbital sodium formulations. Thus, claim 4 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a, optionally further in view of Butler.

Claim 5 of the ’598 Patent depends from claim 1 and further requires the phenobarbital sodium solution to not contain a preservative. ’598 Patent at cl. 5. A POSA, informed by the success of Nobelbar and the associated benefits of avoiding additives, would have been motivated to produce a phenobarbital sodium solution without any preservatives, with a reasonable expectation of success in achieving a stable and safe pharmaceutical product. As discussed above in Sections VII.A.4 and VII.B.1.a.i, Nobelbar demonstrated the feasibility and safety of developing a lyophilized phenobarbital sodium preparation free of additives to address a strong demand for such formulations. The prior art emphasizes the risks associated with additives like benzyl alcohol and propylene glycol, especially for vulnerable populations such as newborns and low birth weight infants, making it preferable to avoid their use in drug products. Kawada 2011 at 205-06; Kawada 2009 at 660-01. The success of Nobelbar in providing a stable lyophilized phenobarbital sodium formulation without any additives, including preservatives, underscores the practicality of this approach. The recognition that “there is no particular safety concern except predictable adverse reactions related to the known pharmacological effects of the

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drug" further supports the notion that excluding preservatives does not compromise safety. Kawada 2011 at 209-10. Therefore, claim 5 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 6 of the '598 Patent depends from claim 1 and further requires the primary drying step to be performed using at increasing temperatures that increase from about −50° C. to about 0° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg. '598 Patent at cl. 6. As discussed above in Sections VII.A.3 and VII.B.1.a.ii, a POSA would have recognized that lyophilization is a widely employed technique for pharmaceutical products and that the lyophilization process involves a primary drying step where heat is applied to the product to initiate sublimation of the frozen water, converting ice directly into vapor without passing through the liquid phase. *See* Brittain 1999 at 215; Craig at 200; Przic at 555; Rey at 3, 16. Given that sublimation requires controlled application of heat, a POSA would understand the need to carefully increase the temperature from around −50° C, the temperature at the freezing step, to around 0°C during the primary drying phase. This gradual increase in temperature facilitates efficient sublimation. Thus, a POSA would have been motivated, with a reasonable expectation of success, to optimize the primary drying step by gradually raising the temperature from about −50° C to about 0°C, recognizing this as a routine optimization step in the lyophilization process.

Furthermore, as discussed above in Section VII.A.5, these specific dosages are well-documented in the pharmaceutical industry. A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg based on the prior art. Phenobarbital sodium injection has

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been available in concentrations of 65 mg/mL and 130 mg/mL with a fill volume of 1 mL, providing precise and effective dosage forms. Hikma at 35 and 62. A POSA would have recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg is both feasible and supported by existing clinical use.

Moreover, a POSA would have been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights. Understanding the need for tailored dosing, a POSA would recognize that different concentrations of phenobarbital sodium solutions, such as 65 mg and 130 mg, would allow for precise dosing based on a patient's weight. Parker describes phenobarbital sodium solutions for injection "in an amount of 15 to 200 mg/mL." Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 65 mg of phenobarbital sodium would be suitable for a neonate with a body weight of about 3.25 kg (approximately 7 pounds), while a vial containing 130 mg would be appropriate for an infant weighing about 6.5 kg (around 14 pounds). Thus, claim 6 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a, optionally further in view of Hikma.

Claim 7 of the '598 Patent depends from claim 1 and further requires the primary drying step to be performed using at constant temperature of about −42° C. when the amount of

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phenobarbital sodium in the container is 200 mg. ’598 Patent at cl. 7. As discussed above in Sections VII.A.3 and VII.B.1.a.ii, a POSA would have recognized that lyophilization is a widely employed technique for pharmaceutical products and that the lyophilization process involves a primary drying step where heat is applied to the product to initiate sublimation of the frozen water, converting ice directly into vapor without passing through the liquid phase. *See* Brittain 1999 at 215; Craig at 200; Przic at 555; Rey at 3, 16. A POSA would understand that controlling the temperature during this step ensures efficient sublimation and prevent the product from degrading. Increasing the temperature from the freezing step at -50°C to a constant -42°C during the primary drying phase would facilitate a controlled sublimation rate while maintaining product stability. Therefore, it would have been routine optimization for a POSA to adjust the temperature to a constant -42°C.

Furthermore, as discussed above in Section VII.A.5, specific dosages of phenobarbital sodium are well-documented in the pharmaceutical industry. A POSA would have been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights, including phenobarbital sodium solutions in amounts of about 200 mg. Understanding the need for tailored dosing, a POSA would recognize that different concentrations of phenobarbital sodium solutions would allow for precise dosing based on a patient’s weight. Parker describes phenobarbital sodium solutions for injection “in an amount of 15 to 200 mg/mL.” Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 200 mg of phenobarbital sodium would be suitable for a baby weighing about 10 kg (around 22 pounds). Thus, claim 7 is obvious over the scope and content of prior art discussed in

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Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 8 of the ’598 Patent depends from claim 1 and further requires the secondary drying step to be performed using at decreasing temperatures that decrease from about 50° C. to about 25° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg. ’598 Patent at cl. 8. As discussed above in Sections VII.A.3 and VII.B.1.a.ii, a POSA would have recognized that lyophilization is a widely employed technique for pharmaceutical products and that the lyophilization process involves a secondary drying step to remove any remaining unfrozen water molecules through desorption. Typically, the temperature during this step is maintained between 25–60°C to effectively facilitate the removal of the remaining water content. Trappler at Tables 1-2, 5; Craig at 201; Pikal at 1807; Broadhead at 340; *see also* Rey at 16, 451. A POSA would understand that decreasing the temperature from about 50°C to about 25°C during the secondary drying step would optimize the desorption process while maintaining the stability and quality of the pharmaceutical product. Given the importance of controlling the drying conditions to achieve the desired moisture content without compromising the integrity of the drug, it would have been routine optimization for a POSA to implement this temperature decrease.

Furthermore, as discussed above in Section VII.A.5, these specific dosages are well-documented in the pharmaceutical industry. A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg based on the prior art. Phenobarbital sodium injection has been available in concentrations of 65 mg/mL and 130 mg/mL with a fill volume of 1 mL, providing precise and effective dosage forms. Hikma at 35 and 62. A POSA would have

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recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 65 mg or 130 mg is both feasible and supported by existing clinical use.

Moreover, a POSA would have been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights. Understanding the need for tailored dosing, a POSA would recognize that different concentrations of phenobarbital sodium solutions, such as 65 mg and 130 mg, would allow for precise dosing based on a patient's weight. Parker describes phenobarbital sodium solutions for injection "in an amount of 15 to 200 mg/mL." Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 65 mg of phenobarbital sodium would be suitable for a neonate with a body weight of about 3.25 kg (approximately 7 pounds), while a vial containing 130 mg would be appropriate for an infant weighing about 6.5 kg (around 14 pounds). Thus, claim 8 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a, optionally further in view of Hikma.

Claim 9 of the '598 Patent depends from claim 1 and further requires the secondary drying step to be performed using at constant temperature of about 35° C. when the amount of phenobarbital sodium in the container is 200 mg. '598 Patent at cl. 9. As discussed above in Sections VII.A.3 and VII.B.1.a.ii, a POSA would have recognized that lyophilization is a widely

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employed technique for pharmaceutical products and that the lyophilization process involves a secondary drying step to remove any remaining unfrozen water molecules through desorption. Typically, the temperature during this step is maintained between 25–60°C to effectively facilitate the removal of the remaining water content. Trappler at Tables 1-2, 5; Craig at 201; Pikal at 1807; Broadhead at 340; *see also* Rey at 16, 451. Given this temperature range, a POSA would understand that maintaining a constant temperature of about 35°C during the secondary drying step would be an effective strategy to ensure the efficient removal of moisture while preventing thermal degradation of the product. Thus, selecting a constant temperature of about 35°C would have been a routine optimization step.

Furthermore, as discussed above in Section VII.A.5, specific dosages of phenobarbital sodium are well-documented in the pharmaceutical industry. A POSA would have been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights, including phenobarbital sodium solutions in amounts of about 200 mg. Understanding the need for tailored dosing, a POSA would recognize that different concentrations of phenobarbital sodium solutions would allow for precise dosing based on a patient's weight. Parker describes phenobarbital sodium solutions for injection "in an amount of 15 to 200 mg/mL." Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 200 mg of phenobarbital sodium would be suitable for a baby weighing about 10 kg (around 22 pounds). Thus, claim 9 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

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Claim 10 of the ’598 Patent depends from claim 1 and further requires the lyophilized amorphous phenobarbital sodium to have an initial moisture content of equal or less than 1.2%. ’598 Patent at cl. 10. As discussed above in Sections VII.A.3 and VII.B.1.a.ii-iii, the primary goal of lyophilization is to remove moisture from the product, ensuring stability and preventing degradation. This process involves a secondary drying phase that specifically aims to reduce the water content to very low levels. The prior art teaches that this secondary drying phase removes any remaining unfrozen water molecules (or residual solvent) through desorption by gradually increasing the product temperature while maintaining low pressure. Brittain 1999 at 215; Przic at 555-56. The objective is to achieve a moisture content typically less than 0.5% in the finished product to ensure product stability. *See* Kern at 23; Rey at 3, 242, 451; Broadhead at 340. Given the clear objective of lyophilization to remove moisture and the documented success in achieving very low moisture content, a POSA would have been motivated to reduce the initial moisture content of lyophilized phenobarbital sodium to 1.2% or less. A POSA would have also had a reasonable expectation of success in achieving this moisture content as the prior art consistently supports this approach, indicating that such low moisture levels are feasible and beneficial for maintaining the stability and preventing the degradation of the lyophilized product. Therefore, claim 10 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 11 of the ’598 Patent depends from claim 1 and further requires the lyophilized amorphous phenobarbital sodium to have an initial moisture content of equal or less than 1.0%. ’598 Patent at cl. 11. As discussed above in Sections VII.A.3 and VII.B.1.a.ii-iii, the primary goal of lyophilization is to remove moisture from the product, ensuring stability and

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preventing degradation. This process involves a secondary drying phase that specifically aims to reduce the water content to very low levels. The prior art teaches that this secondary drying phase removes any remaining unfrozen water molecules (or residual solvent) through desorption by gradually increasing the product temperature while maintaining low pressure. Brittain 1999 at 215; Przic at 555-56. The objective is to achieve a moisture content typically less than 0.5% in the finished product to ensure product stability. *See* Kern at 23; Rey at 3, 242; Broadhead at 340. Given the clear objective of lyophilization to remove moisture and the documented success in achieving very low moisture content, a POSA would have been motivated to reduce the initial moisture content of lyophilized phenobarbital sodium to 1.0% or less. A POSA would have also had a reasonable expectation of success in achieving this moisture content as the prior art consistently supports this approach, indicating that such low moisture levels are feasible and beneficial for maintaining the stability and preventing the degradation of the lyophilized product. Therefore, claim 11 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 12 of the ’598 Patent depends from claim 1 and further requires the lyophilized amorphous phenobarbital sodium to form, upon storage over 3 months, no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. ’598 Patent at cl. 12. As discussed above in Sections VII.A.2 and VII.B.1.a.iv, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PEAU. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.1.a.ii,

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VII.B.1.a.iv-v; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU in the final product. Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters, would form no more than 0.1% PEAU when reconstituted in an aqueous solution upon storage over three months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Therefore, claim 12 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 13 of the '598 Patent depends from claim 1 and further requires the lyophilized amorphous phenobarbital sodium to form, upon storage over 3 months, no detectable quantities of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution. '598 Patent at cl. 13. As discussed above in Sections VII.A.2 and VII.B.1.a.iv, phenobarbital sodium was known to degrade through various pathways,

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particularly in the presence of water, resulting in the formation of harmful impurities such as 2EPMM and PBG. Parker at [0004], [0006], [0007], Table 1. Regulatory guidelines and industry standards emphasize the need to control impurities in pharmaceutical formulations to ensure the safety of APIs. *See supra* Sections VII.A.2 and VII.B.1.a.iv. For example, the EMEA Guideline, ICH Q3A(R2), and ICH Q3B(R2) stress the importance of identifying and controlling actual and potential impurities that may arise during synthesis, purification, and storage. EMEA Guideline at 4; ICH Q3A(R2) at § 3; ICH Q3B(R2) at § 2. In the context of phenobarbital sodium, the degradation products 2EPMM and PBG are well-documented, highlighting the necessity of stringent impurity control. *See* Parker at [0004], [0006], [0007], Table 1.

Strategies to minimize the presence of impurities include the use of stable formulations that prevent the formation of significant amounts of degradation products during storage. The success of formulations like Nobelbar, which reported "no clear changes" in stability during long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies, underscores the effectiveness of lyophilization in producing stable products with minimal degradation. Deliberation Results Report at 5. These stability studies confirm the reliability and effectiveness of lyophilization in producing a stable lyophilized amorphous phenobarbital sodium compositions with minimal degradation. Therefore, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters, would form no detectable quantities of 2EPMM or PBG when reconstituted in an aqueous solution upon storage over three months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Consequently, claim 13 is obvious

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over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

Claim 14 of the ’598 Patent depends from claim 1 and further requires the 3-month storage to be at 40° C. and 75% relative humidity. ’598 Patent at cl. 14. As discussed in Section VII.A.4, the stability of finished pharmaceutical products is important for ensuring their efficacy and safety over time. Stability testing is conducted under standardized conditions, including specific temperature and relative humidity, to provide reliable data on the product’s shelf life. For accelerated studies of finished pharmaceutical products, the storage conditions are typically 40°C ± 2°C/75% RH ± 5% RH for six months. Annex 10 at Table 2.2.7.1; EMEA ICH Topic Q1A at 3, 6; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14. This condition is well-documented in the prior art and regulatory guidelines, indicating its acceptance as a reliable method to simulate long-term storage conditions in a shorter timeframe. Given the established protocols and the significance of these standardized stability testing conditions, it would have been obvious for a POSA to employ the three-month storage condition at 40°C and 75% relative humidity for lyophilized amorphous phenobarbital sodium to ensure its stability and efficacy. Therefore, claim 14 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a, optionally further in view of Annex 10, EMEA ICH Topic Q1A, and/or FDA Guidance for Industry Q1A(R2).

Claim 15 of the ’598 Patent depends from claim 1 and further requires the lyophilized amorphous phenobarbital sodium composition to contain at least 98% lyophilized amorphous phenobarbital sodium. ’598 Patent at cl. 15. As discussed above in Section VII.A.4, the prior art

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and market examples, such as Nobelbar, demonstrate that a lyophilized amorphous phenobarbital sodium composition containing at least 98% lyophilized amorphous phenobarbital sodium is a feasible and practical approach. Nobelbar has been on the market since December 2008 and is known for its efficacy and safety. Kawada 2011 at 209-10. Nobelbar is specifically noted for being "a lyophilized injection composed of ***drug substance only***, without additives," which directly supports the feasibility of achieving a composition with at least 98% lyophilized phenobarbital sodium. Deliberation Results Report at 5 (emphasis added); *see also* Kawada 2011 at 205. The absence of these additives in Nobelbar aligns with the safety and stability requirements for neonatal and pediatric use. Kawada 2011 at 205-06; Kawada 2009 at 660-01. Given the documented success of stable formulations like Nobelbar, a POSA would recognize that it is not only possible but also advantageous to develop a lyophilized amorphous phenobarbital sodium composition containing at least 98% of the active ingredient. The practicality, stability, and safety of Nobelbar exemplify the benefits of such high-purity formulations, motivating a POSA to pursue this approach with a reasonable expectation of success. Therefore, claim 15 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.1.a.

c. Identification of Prior Art

The tables below list prior art that anticipates and/or renders obvious one or more of claims 1-15 of the '598 Patent. The attached claim charts in Exhibits A-1 to A-7 demonstrate where each limitation of the claims is found in, either expressly or inherently in the larger context of the passage, or rendered obvious by, certain of the references listed below, as

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understood by a person having ordinary skill in the art. The following patents, publications, products and/or services are prior art under at least 35 U.S.C. §§ 102(a), (b) or (d).

i. Prior Art References, Patents, Patent Publications, and Non-Patent Publications to the Claims 1-15 of the '598 Patent

Chart	Reference	Filing Date	Date of Issue or Publication	Citation	Claims
A-1	Nobelbar		2008	Nobelbar	Obvious: 1-15
A-2	Gardenal		As early as 1992	Gardenal	Obvious: 1-15
A-3	Joseph Herschel Kern, *Freeze Drying as a Method of Processing Some Pharmaceutical Products* (1954) (dissertation for Doctor of Philosophy, Ohio State University)		1954	Kern	Obvious: 1-15
A-4	Małgorzata Sznitowska et al., *The physical characteristics of lyophilized tablets containing a model drug in different chemical forms and concentrations*, 62(1) ACTA POLONIAE PHARM. 25 (2009)		2009	Sznitowska	Obvious: 1-15
A-5	U.S. Patent Application Publication No. US 2017/0143719	Nov. 18, 2016	May 25, 2017	Parker	Obvious: 1-15
A-6	*2018 Injectable Product Catalog*, HIKMA (2018)		2018	Hikma	Obvious: 1-15

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ii. Prior Art Pharmaceutical Compositions/Products To The Claims 1-15 of the '598 Patent

Sun further identifies the commercial embodiments of the inventions described in Exhibits A-1 to A-6, to the extent those pharmaceutical compositions or products were on sale or in public use before the priority date of the '598 Patent, and all publicly available information relating to such products or properties inherent to such products. Moreover, on information and belief, Nobelpharma Co., Ltd. ("Nobelpharma") and other companies sold, offered for sale, and/or publicly used products incorporating Nobelpharma's Nobelbar ("Nobelbar") that constitutes prior art to the '598 Patent. Chart A-1 demonstrates where each limitation of the claims is found in Nobelbar.

Moreover, on information and belief, companies sold, offered for sale, and/or publicly used products incorporating Gardenal that constitutes prior art to the '598 Patent. Chart A-2 demonstrates where each limitation of the claims is found in Gardenal.

iii. Obviousness Combinations

A person having ordinary skill in the art would have been motivated to modify or combine the references described in attached Exhibits A-1 to A-6 as listed below, or further as shown in the exemplary omnibus reference Exhibit A-7, and for the reasons described below.

Reference	In Combination With	Claims
Nobelbar	Parker	1-15
	Rey	1-15
	Brittain 1999	1-15
	Przic	1-15
	Sandhyarani	1-15
	FDA_7/93	1-15
	Pikal	1-15
	Craig	1-15
	Bernstein	1-15
	Einfalt	1-15
	Yu	1-15
	Broadhead	1-15

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Reference	In Combination With	Claims
	Trappler	1-15
	Parker and Rey	1-15
	Parker and Brittain 1999	1-15
	Parker and Przic	1-15
	Parker and Sandhyarani	1-15
	Parker and FDA_7/93	1-15
	Parker and Pikal	1-15
	Parker and Craig	1-15
	Parker and Bernstein	1-15
	Parker and Einfalt	1-15
	Parker and Yu	1-15
	Parker and Broadhead	1-15
	Parker and Trappler	1-15
	EMEA Guideline	1-15
	ICH Q3A(R2)	1-15
	ICH Q3B(R2)	1-15
	Anderson 2000	1-15
	Anderson 2012	1-15
	Liu	1-15
	Prabu	1-15
	Parker and EMEA Guideline	1-15
	Parker and ICH Q3A(R2)	1-15
	Parker and ICH Q3B(R2)	1-15
	Parker and Anderson 2000	1-15
	Parker and Anderson 2012	1-15
	Parker and Liu	1-15
	Parker and Prabu	1-15
	Parker and Rey and EMEA Guideline	1-15
	Parker and Rey and ICH Q3A(R2)	1-15
	Parker and Rey and ICH Q3B(R2)	1-15
	Parker and Rey and Anderson 2000	1-15
	Parker and Rey and Anderson 2012	1-15
	Parker and Rey and Liu	1-15
	Parker and Rey and Prabu	1-15
	Parker and Brittain 1999 and EMEA Guideline	1-15
	Parker and Brittain 1999 and ICH Q3A(R2)	1-15
	Parker and Brittain 1999 and ICH Q3B(R2)	1-15
	Parker and Brittain 1999 and Anderson 2000	1-15
	Parker and Brittain 1999 and Anderson 2012	1-15
	Parker and Brittain 1999 and Liu	1-15
	Parker and Brittain 1999 and Prabu	1-15
	Parker and Przic and EMEA Guideline	1-15
	Parker and Przic and ICH Q3A(R2)	1-15
	Parker and Przic and ICH Q3B(R2)	1-15
	Parker and Przic and Anderson 2000	1-15

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Reference	In Combination With	Claims
	Parker and Przic and Anderson 2012	1-15
	Parker and Przic and Liu	1-15
	Parker and Przic and Prabu	1-15
	Parker and Sandhyarani and EMEA Guideline	1-15
	Parker and Sandhyarani and ICH Q3A(R2)	1-15
	Parker and Sandhyarani and ICH Q3B(R2)	1-15
	Parker and Sandhyarani and Anderson 2000	1-15
	Parker and Sandhyarani and Anderson 2012	1-15
	Parker and Sandhyarani and Liu	1-15
	Parker and Sandhyarani and Prabu	1-15
	Parker and FDA_7/93 and EMEA Guideline	1-15
	Parker and FDA_7/93 and ICH Q3A(R2)	1-15
	Parker and FDA_7/93 and ICH Q3B(R2)	1-15
	Parker and FDA_7/93 and Anderson 2000	1-15
	Parker and FDA_7/93 and Anderson 2012	1-15
	Parker and FDA_7/93 and Liu	1-15
	Parker and FDA_7/93 and Prabu	1-15
	Parker and Pikal and EMEA Guideline	1-15
	Parker and Pikal and ICH Q3A(R2)	1-15
	Parker and Pikal and ICH Q3B(R2)	1-15
	Parker and Pikal and Anderson 2000	1-15
	Parker and Pikal and Anderson 2012	1-15
	Parker and Pikal and Liu	1-15
	Parker and Pikal and Prabu	1-15
	Parker and Craig and EMEA Guideline	1-15
	Parker and Craig and ICH Q3A(R2)	1-15
	Parker and Craig and ICH Q3B(R2)	1-15
	Parker and Craig and Anderson 2000	1-15
	Parker and Craig and Anderson 2012	1-15
	Parker and Craig and Liu	1-15
	Parker and Craig and Prabu	1-15
	Parker and Bernstein and EMEA Guideline	1-15
	Parker and Bernstein and ICH Q3A(R2)	1-15
	Parker and Bernstein and ICH Q3B(R2)	1-15
	Parker and Bernstein and Anderson 2000	1-15
	Parker and Bernstein and Anderson 2012	1-15
	Parker and Bernstein and Liu	1-15
	Parker and Bernstein and Prabu	1-15
	Parker and Einfalt and EMEA Guideline	1-15
	Parker and Einfalt and ICH Q3A(R2)	1-15
	Parker and Einfalt and ICH Q3B(R2)	1-15
	Parker and Einfalt and Anderson 2000	1-15
	Parker and Einfalt and Anderson 2012	1-15
	Parker and Einfalt and Liu	1-15
	Parker and Einfalt and Prabu	1-15

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Reference	In Combination With	Claims
	Parker and Yu and EMEA Guideline	1-15
	Parker and Yu and ICH Q3A(R2)	1-15
	Parker and Yu and ICH Q3B(R2)	1-15
	Parker and Yu and Anderson 2000	1-15
	Parker and Yu and Anderson 2012	1-15
	Parker and Yu and Liu	1-15
	Parker and Yu and Prabu	1-15
	Parker and Broadhead and EMEA Guideline	1-15
	Parker and Broadhead and ICH Q3A(R2)	1-15
	Parker and Broadhead and ICH Q3B(R2)	1-15
	Parker and Broadhead and Anderson 2000	1-15
	Parker and Broadhead and Anderson 2012	1-15
	Parker and Broadhead and Liu	1-15
	Parker and Broadhead and Prabu	1-15
	Parker and Trappler and EMEA Guideline	1-15
	Parker and Trappler and ICH Q3A(R2)	1-15
	Parker and Trappler and ICH Q3B(R2)	1-15
	Parker and Trappler and Anderson 2000	1-15
	Parker and Trappler and Anderson 2012	1-15
	Parker and Trappler and Liu	1-15
	Parker and Trappler and Prabu	1-15
	Butler	1-15
	Parker and Butler	1-15
	Rey and Butler	1-15
	Brittain 1999 and Butler	1-15
	Przic and Butler	1-15
	Sandhyarani and Butler	1-15
	FDA_7/93 and Butler	1-15
	Pikal and Butler	1-15
	Craig and Butler	1-15
	Bernstein and Butler	1-15
	Einfalt and Butler	1-15
	Yu and Butler	1-15
	Broadhead and Butler	1-15
	Trappler and Butler	1-15
	Parker and Rey and Butler	1-15
	Parker and Brittain 1999 and Butler	1-15
	Parker and Przic and Butler	1-15
	Parker and Sandhyarani and Butler	1-15
	Parker and FDA_7/93 and Butler	1-15
	Parker and Pikal and Butler	1-15
	Parker and Craig and Butler	1-15
	Parker and Bernstein and Butler	1-15
	Parker and Einfalt and Butler	1-15
	Parker and Yu and Butler	1-15

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Reference	In Combination With	Claims
	Parker and Broadhead and Butler	1-15
	Parker and Trappler and Butler	1-15
	EMEA Guideline and Butler	1-15
	ICH Q3A(R2) and Butler	1-15
	ICH Q3B(R2) and Butler	1-15
	Anderson 2000 and Butler	1-15
	Anderson 2012 and Butler	1-15
	Liu and Butler	1-15
	Prabu and Butler	1-15
	Parker and EMEA Guideline and Butler	1-15
	Parker and ICH Q3A(R2) and Butler	1-15
	Parker and ICH Q3B(R2) and Butler	1-15
	Parker and Anderson 2000 and Butler	1-15
	Parker and Anderson 2012 and Butler	1-15
	Parker and Liu and Butler	1-15
	Parker and Prabu and Butler	1-15
	Parker and Rey and EMEA Guideline and Butler	1-15
	Parker and Rey and ICH Q3A(R2) and Butler	1-15
	Parker and Rey and ICH Q3B(R2) and Butler	1-15
	Parker and Rey and Anderson 2000 and Butler	1-15
	Parker and Rey and Anderson 2012 and Butler	1-15
	Parker and Rey and Liu and Butler	1-15
	Parker and Rey and Prabu and Butler	1-15
	Parker and Brittain 1999 and EMEA Guideline and Butler	1-15
	Parker and Brittain 1999 and ICH Q3A(R2) and Butler	1-15
	Parker and Brittain 1999 and ICH Q3B(R2) and Butler	1-15
	Parker and Brittain 1999 and Anderson 2000 and Butler	1-15
	Parker and Brittain 1999 and Anderson 2012 and Butler	1-15
	Parker and Brittain 1999 and Liu and Butler	1-15
	Parker and Brittain 1999 and Prabu and Butler	1-15
	Parker and Przic and EMEA Guideline and Butler	1-15
	Parker and Przic and ICH Q3A(R2) and Butler	1-15
	Parker and Przic and ICH Q3B(R2) and Butler	1-15
	Parker and Przic and Anderson 2000 and Butler	1-15
	Parker and Przic and Anderson 2012 and Butler	1-15
	Parker and Przic and Liu and Butler	1-15
	Parker and Przic and Prabu and Butler	1-15
	Parker and Sandhyarani and EMEA Guideline and Butler	1-15
	Parker and Sandhyarani and ICH Q3A(R2) and Butler	1-15
	Parker and Sandhyarani and ICH Q3B(R2) and Butler	1-15
	Parker and Sandhyarani and Anderson 2000 and Butler	1-15
	Parker and Sandhyarani and Anderson 2012 and Butler	1-15
	Parker and Sandhyarani and Liu and Butler	1-15
	Parker and Sandhyarani and Prabu and Butler	1-15
	Parker and FDA_7/93 and EMEA Guideline and Butler	1-15

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	Parker and Broadhead and EMEA Guideline and Hikma	1-15
	Parker and Broadhead and ICH Q3A(R2) and Hikma	1-15
	Parker and Broadhead and ICH Q3B(R2) and Hikma	1-15
	Parker and Broadhead and Anderson 2000 and Hikma	1-15
	Parker and Broadhead and Anderson 2012 and Hikma	1-15
	Parker and Broadhead and Liu and Hikma	1-15
	Parker and Broadhead and Prabu and Hikma	1-15
	Parker and Trappler and EMEA Guideline and Hikma	1-15
	Parker and Trappler and ICH Q3A(R2) and Hikma	1-15

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	Parker and Trappler and ICH Q3B(R2) and Hikma	1-15
	Parker and Trappler and Anderson 2000 and Hikma	1-15
	Parker and Trappler and Anderson 2012 and Hikma	1-15
	Parker and Trappler and Liu and Hikma	1-15
	Parker and Trappler and Prabu and Hikma	1-15
	Butler and Hikma	1-15
	Parker and Butler and Hikma	1-15
	Rey and Butler and Hikma	1-15
	Brittain 1999 and Butler and Hikma	1-15
	Przic and Butler and Hikma	1-15
	Sandhyarani and Butler and Hikma	1-15
	FDA_7/93 and Butler and Hikma	1-15
	Pikal and Butler and Hikma	1-15
	Craig and Butler and Hikma	1-15
	Bernstein and Butler and Hikma	1-15
	Einfalt and Butler and Hikma	1-15
	Yu and Butler and Hikma	1-15
	Broadhead and Butler and Hikma	1-15
	Trappler and Butler and Hikma	1-15
	Parker and Rey and Butler and Hikma	1-15
	Parker and Brittain 1999 and Butler and Hikma	1-15
	Parker and Przic and Butler and Hikma	1-15
	Parker and Sandhyarani and Butler and Hikma	1-15
	Parker and FDA_7/93 and Butler and Hikma	1-15
	Parker and Pikal and Butler and Hikma	1-15
	Parker and Craig and Butler and Hikma	1-15
	Parker and Bernstein and Butler and Hikma	1-15
	Parker and Einfalt and Butler and Hikma	1-15
	Parker and Yu and Butler and Hikma	1-15
	Parker and Broadhead and Butler and Hikma	1-15
	Parker and Trappler and Butler and Hikma	1-15
	EMEA Guideline and Butler and Hikma	1-15
	ICH Q3A(R2) and Butler and Hikma	1-15
	ICH Q3B(R2) and Butler and Hikma	1-15
	Anderson 2000 and Butler and Hikma	1-15
	Anderson 2012 and Butler and Hikma	1-15
	Liu and Butler and Hikma	1-15
	Prabu and Butler and Hikma	1-15
	Parker and EMEA Guideline and Butler and Hikma	1-15
	Parker and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Anderson 2000 and Butler and Hikma	1-15
	Parker and Anderson 2012 and Butler and Hikma	1-15
	Parker and Liu and Butler and Hikma	1-15
	Parker and Prabu and Butler and Hikma	1-15

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	Parker and Rey and EMEA Guideline and Butler and Hikma	1-15
	Parker and Rey and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Rey and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Rey and Anderson 2000 and Butler and Hikma	1-15
	Parker and Rey and Anderson 2012 and Butler and Hikma	1-15
	Parker and Rey and Liu and Butler and Hikma	1-15
	Parker and Rey and Prabu and Butler and Hikma	1-15
	Parker and Brittain 1999 and EMEA Guideline and Butler and Hikma	1-15 1-15
	Parker and Brittain 1999 and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Brittain 1999 and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Brittain 1999 and Anderson 2000 and Butler and Hikma	1-15
	Parker and Brittain 1999 and Anderson 2012 and Butler and Hikma	1-15
	Parker and Brittain 1999 and Liu and Butler and Hikma	1-15
	Parker and Brittain 1999 and Prabu and Butler and Hikma	1-15
	Parker and Przic and EMEA Guideline and Butler and Hikma	1-15
	Parker and Przic and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Przic and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Przic and Anderson 2000 and Butler and Hikma	1-15
	Parker and Przic and Anderson 2012 and Butler and Hikma	1-15
	Parker and Przic and Liu and Butler and Hikma	1-15
	Parker and Przic and Prabu and Butler and Hikma	1-15
	Parker and Sandhyarani and EMEA Guideline and Butler and Hikma	1-15 1-15
	Parker and Sandhyarani and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Sandhyarani and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Sandhyarani and Anderson 2000 and Butler and Hikma	1-15
	Parker and Sandhyarani and Anderson 2012 and Butler and Hikma	1-15
	Parker and Sandhyarani and Liu and Butler and Hikma	1-15
	Parker and Sandhyarani and Prabu and Butler and Hikma	1-15
	Parker and FDA_7/93 and EMEA Guideline and Butler and Hikma	1-15
	Parker and FDA_7/93 and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and FDA_7/93 and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and FDA_7/93 and Anderson 2000 and Butler and Hikma	1-15
	Parker and FDA_7/93 and Anderson 2012 and Butler and Hikma	1-15
	Parker and FDA_7/93 and Liu and Butler and Hikma	1-15
	Parker and FDA_7/93 and Prabu and Butler and Hikma	1-15
	Parker and Pikal and EMEA Guideline and Butler and Hikma	1-15
	Parker and Pikal and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Pikal and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Pikal and Anderson 2000 and Butler and Hikma	1-15
	Parker and Pikal and Anderson 2012 and Butler and Hikma	1-15
	Parker and Pikal and Liu and Butler and Hikma	1-15
	Parker and Pikal and Prabu and Butler and Hikma	1-15
	Parker and Craig and EMEA Guideline and Butler and Hikma	1-15

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	Parker and Craig and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Craig and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Craig and Anderson 2000 and Butler and Hikma	1-15
	Parker and Craig and Anderson 2012 and Butler and Hikma	1-15
	Parker and Craig and Liu and Butler and Hikma	1-15
	Parker and Craig and Prabu and Butler and Hikma	1-15
	Parker and Bernstein and EMEA Guideline and Butler and Hikma	1-15
	Parker and Bernstein and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Bernstein and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Bernstein and Anderson 2000 and Butler and Hikma	1-15
	Parker and Bernstein and Anderson 2012 and Butler and Hikma	1-15
	Parker and Bernstein and Liu and Butler and Hikma	1-15
	Parker and Bernstein and Prabu and Butler and Hikma	1-15
	Parker and Einfalt and EMEA Guideline and Butler and Hikma	1-15
	Parker and Einfalt and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Einfalt and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Einfalt and Anderson 2000 and Butler and Hikma	1-15
	Parker and Einfalt and Anderson 2012 and Butler and Hikma	1-15
	Parker and Einfalt and Liu and Butler and Hikma	1-15
	Parker and Einfalt and Prabu and Butler and Hikma	1-15
	Parker and Yu and EMEA Guideline and Butler and Hikma	1-15
	Parker and Yu and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Yu and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Yu and Anderson 2000 and Butler and Hikma	1-15
	Parker and Yu and Anderson 2012 and Butler and Hikma	1-15
	Parker and Yu and Liu and Butler and Hikma	1-15
	Parker and Yu and Prabu and Butler and Hikma	1-15
	Parker and Broadhead and EMEA Guideline and Butler and Hikma	1-15
	Parker and Broadhead and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Broadhead and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Broadhead and Anderson 2000 and Butler and Hikma	1-15
	Parker and Broadhead and Anderson 2012 and Butler and Hikma	1-15
	Parker and Broadhead and Liu and Butler and Hikma	1-15
	Parker and Broadhead and Prabu and Butler and Hikma	1-15
	Parker and Trappler and EMEA Guideline and Butler and Hikma	1-15
	Parker and Trappler and ICH Q3A(R2) and Butler and Hikma	1-15
	Parker and Trappler and ICH Q3B(R2) and Butler and Hikma	1-15
	Parker and Trappler and Anderson 2000 and Butler and Hikma	1-15
	Parker and Trappler and Anderson 2012 and Butler and Hikma	1-15
	Parker and Trappler and Liu and Butler and Hikma	1-15
	Parker and Trappler and Prabu and Butler and Hikma	1-15

A person having ordinary skill in the art at the time of filing of the ’598 Patent would also have understood the references listed above, alone or in combination, to contain explicit and/or

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implicit teaching, suggestion, and/or rationales to combine them. It would have been obvious to a person of ordinary skill in the art at the time of the alleged invention to combine a reference with one or more of the other references for the following reasons:

- Combining the prior art limitations according to known methods would have yielded predictable results.
- Simple substitution of one known limitation for another would have yielded predictable results.
- Use of known technique to improve similar pharmaceutical compositions and products in the same way would have been obvious.
- Applying a known technique to a known pharmaceutical composition and product ready for improvement would have yielded predictable results.
- References disclosing these concepts teach the beneficial utility of them, including as cited in the claim charts submitted herewith.

In addition, a person of ordinary skill in the art would have been motivated to make the combinations based on general industry trends and other considerations discussed in connection with the state of the art. For example, as explained in Section VII.A, which describes the state of the art prior to the alleged dates of alleged inventions in the ’598 Patent, phenobarbital and phenobarbital sodium were widely known and used. Specifically, phenobarbital sodium was known to degrade due to residual water in the composition and/or atmosphere, producing PEAU, 2EPMM, and PBG. Moreover, lyophilization of pharmaceutical compositions and products was well-known and extensively utilized in the industry, particularly for products intended for parenteral administration. As explained in Section VII.B.1.a.i, a POSA would have known that lyophilized phenobarbital sodium drug products were tested as model drugs and were already on

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the market. Furthermore, as described in Sections VII.B.1.a.ii-iii, a POSA would have applied widely used lyophilization parameters and would have known that the resulting lyophilized phenobarbital sodium products would be amorphous with low moisture content. Finally, a POSA would have been motivated, with a reasonable expectation of success, to reduce degradants as much as reasonably practicable.

A person of ordinary skill in the art at the time of the alleged invention would have combined the references because each generally relates to similar technology. Moreover, to the extent the '598 Patent identifies any needed improvement in the art, the references provide known techniques that would yield the required improvement, and given the finite number of techniques identified, it would have been obvious to try those approaches with a reasonable expectation of success.

The combinations of references provided are exemplary and are not intended to be exhaustive. Additional obviousness combinations of the references identified here are possible, and Sun may rely on such combination(s) in this litigation. In particular, Sun is currently unaware of Plaintiff's allegations with respect to the level of skill in the art and the qualifications of the typical person of ordinary skill in the art. Further, Plaintiff's infringement contentions are largely devoid of substance making it difficult to determine Plaintiff's view as to the metes and bounds of numerous elements and how they apply to Sun's Product and, thus, the prior art. Sun is also unaware of the extent, if any, to which Plaintiff may contend that limitations of the claims at issue are not disclosed in the prior art identified by Sun as anticipatory, and the extent to which Plaintiff will contend that elements not disclosed in the Asserted Patent specifications would have been known to persons of skill in the art. And Sun does not yet know how the Court will construe terms in the claims. Sun is also continuing its investigation of the universe of prior

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art to identify potential prior art pharmaceutical compositions and products, publications related to those pharmaceutical compositions and products, and third parties that may have information about those pharmaceutical compositions and products. Plaintiff may also be in possession of prior art that Sun may receive as discovery progresses in this case. Sun reserves the right to amend and supplement these contentions to identify other prior art and combinations rendering the claims obvious.

2. The Claims of the ’076 Patent Are Obvious in View of the Prior Art

The references described in Sections VI and VII.A above, along with the common knowledge in the art as of June 30, 2022[10], render all of the claims of the ’076 Patent obvious under 35 U.S.C. § 103.

The motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. § 103 can be found in the references identified above in Sections VI and VII.A. To the extent that any limitation is not explicitly disclosed in a prior art reference discussed above, it would have been achieved through routine optimization by one of ordinary skill in the art. *See, e.g.*, *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980). For at least these additional reasons, any such limitation would have been rendered obvious as well. *See also KSR*, 550 U.S. at 416-17. Common sense, design incentives, market forces, and the background knowledge possessed by a POSA provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the subject matter of the claims of the ’076 Patent.

[10] As discussed in Section III.B.4, the priority date of the ’076 Patent is June 30, 2022. The common knowledge in the art would also support the invalidity of all of the claims of the Patents-in-Suit even if Plaintiff successfully asserts an earlier priority date.

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a. Obviousness of Independent Claims 1 and 7

The state of the art from Section VII.A is incorporated herein, as is the scope and content of the prior art from Section VI. The obviousness analysis for the '598 Patent in Section VII.B.1 is also incorporated herein. Sun also presents the following analysis specific to claims 1 and 7 of the '076 Patent.

Independent claim 1 of the '076 Patent is directed to a storage stable pharmaceutical product comprising a composition with a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium in a single use dose vial, wherein the composition is sterile and lyophilized and comprises no less than 98% phenobarbital sodium. '076 Patent at cl. 1.

Independent claim 7 of the '076 Patent is directed to a pharmaceutical product comprising a composition with a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium in a single use dose vial, wherein the composition is sterile and lyophilized, comprises no less than 98% phenobarbital sodium, ***and*** has the property that when stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU). '076 Patent at cl. 7.

A POSA would have been motivated and would have had a reasonable expectation of success in producing such pharmaceutical products.

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i. A POSA Would Have Known that Lyophilized Phenobarbital Sodium Drug Products Were Tested as Model Drugs and Already on the Market and Would Have Been Motivated and Would Have Had a Reasonable Expectation of Success in Producing a Storage-Stable Pharmaceutical Product Comprising Lyophilized Phenobarbital Sodium Composition

At the time of the alleged invention, a POSA would have been well aware of the widespread use and established properties of phenobarbital sodium. *See supra* Section VII.A.1. Phenobarbital sodium, the sodium salt of phenobarbital, had been approved for subcutaneous and intramuscular use since 1949, and was recognized for its anticonvulsant, hypnotic, and sedative effects. Deliberation Results Report at 3. The physical and chemical properties of phenobarbital sodium, including its solubility and stability characteristics, were well-documented. *See* USP at 2493, 5665-66; West-Ward at § 9; Deliberation Results Report at 4. This extensive prior art would have provided important information for developing stable pharmaceutical formulations.

The lyophilization of phenobarbital sodium had been extensively studied to create stable formulations. Studies demonstrated that lyophilized phenobarbital sodium served as a model drug for lyophilized tablets, showing better mechanical strength and reduced plasticity and porosity at higher doses. Kern at 81; Sznitowska at Abstract. Additionally, lyophilized phenobarbital sodium products like Nobelbar had been marketed, proving the efficacy and safety of such formulations. *See, e.g.*, Kawada 2011 at 210; Deliberation Results Report at 2. Nobelbar, Japan's first phenobarbital drug for intravenous injection, addressed the demand for a phenobarbital preparation free of additives and demonstrated stability over extensive testing periods. Kawada 2011 at 205-06; Kawada 2009 at 660-01; Deliberation Results Report at 5. Unlike other phenobarbital sodium products, which contain organic solvents, Nobelbar was free

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of such additives, meeting a need for phenobarbital preparations for neonatal and pediatric use. Kawada 2011 at 205-06; Kawada 2009 at 660-01.

A POSA would understand the significance of Nobelbar's formulation, which excludes organic solvents, due to the documented instability of phenobarbital sodium in water and the concern about organic solvents in pediatric and neonatal applications. *See supra* Section VII.A.2. Nobelbar's success in the market highlighted the feasibility and advantages of producing a storage stable lyophilized phenobarbital sodium composition free of organic solvents, thus motivating further development in this direction. *See* Kawada 2011 at 205-06; Kawada 2009 at 660-01.

Moreover, other phenobarbital sodium solutions, such as Parker's and Shah's formulations, provided stable solutions for injection without generating significant amounts of impurities during extended storage. *See generally* Parker; Shah. Shah provides a lyophilized pharmaceutical composition of phenobarbital sodium that has stability over a lengthy shelf life. Shah at Abstract, 1:14-16, 2:39-45, 5:6-10, 6:65-67, cls. 1, 3, 8, 25.

Another example, Gardenal, used for subcutaneous or intramuscular injections, further exemplified the application of lyophilization in producing storage stable phenobarbital sodium products. Bertaux at 656; Fournier at 1584. Stability studies under standardized conditions confirmed the long-term stability and quality of these products, ensuring their efficacy and safety over time. *See* Annex 10 at Tables 2.1.7.1, 2.2.7.1; EMEA ICH Topic Q1A at 3, 6; FDA Guidance for Industry Q1A(R2) at 4-7, 9-14; FDA_7/93.

Furthermore, the '608 Publication also discloses storage-stable lyophilized compositions of phenobarbital sodium salt. *E.g.*, '608 Publication at Abstract, [0002] ("The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity

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that are essentially void of impurities upon reconstitution in water."). The '608 Publication teaches compositions of, methods of producing, and use of a lyophilized amorphous phenobarbital sodium formulation with high storage stability and purity. *Id.* at [0010]. Such methods include "adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution." *Id.* at [0013]. To adjust the pH of the phenobarbital sodium solution, the '608 Publication suggests using hydrochloric acid (HCl) or Sodium Hydroxide (NaOH). *Id.* at [0077]. The '608 Publication also notes that "[i]n preferred embodiments, the Water for Injection is sparged with nitrogen [for at least 30 minutes] prior to adding the Phenobarbital Sodium" and "[i]n additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium." *Id.* at [0014]. The '608 Publication further discloses filtering the phenobarbital sodium solution prior to lyophilization. *Id.* at [0018].

Consequently, the extensive prior art and documented properties of phenobarbital sodium, along with the successful development and market presence of lyophilized phenobarbital sodium products such as the '608 Publication, Shah, Nobelbar, and Gardenal, clearly demonstrate that a POSA would have been aware of the viability and effectiveness of lyophilizing phenobarbital sodium into a storage stable pharmaceutical product. Thus, a POSA would have been motivated, with a reasonable expectation of success, to produce such a storage-stable lyophilized phenobarbital sodium composition.

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ii. A POSA Would Have Recognized that Lyophilization was a Technique Which Was Widely Employed for Pharmaceutical Products and Would Have Recognized that Lyophilized Phenobarbital Sodium Drug Compositions Would be Sterile

A POSA would have recognized that lyophilization was a widely employed technique in the pharmaceutical industry, particularly for creating stable, dry powders from aqueous solutions. *See supra* Sections VII.A.3, VII.B.1.a.ii. This technique, also known as freeze-drying, involves three steps: freezing, primary drying, and secondary drying. *See, e.g.*, Brittain 1999 at 214-15; Przic at 552-54; Kern at 2, 19; Sandhyarani at Abstract; FDA_7/93; Broadhead at 340; *see generally* Rey. Each step uses specific parameters of temperature, pressure, and duration to ensure the stability and efficacy of the final product. The '608 Publication also describes lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial, and 200 mg/vial of phenobarbital sodium compositions. *See* '608 Publication at [0123], Table 15.

Lyophilization is particularly useful for compounds susceptible to decomposition by water, as it significantly reduces water-based degradation. *See* Pikal at 1807; FDA_7/93; Rey at 82. The process involves sealing vials in a freeze dryer, which allows for precise moisture control and maintains the sterility and particle-free characteristics of the product. Przic at 553; Pikal at 1808. This method is advantageous for products whose stability is adversely affected by residual moisture or oxygen. Brittain 1999 at 213-14; Pikal at 1808; Kern at 107. Lyophilization maintains sterility much more effectively than other processes involving dry powder handling, such as spray drying or bulk crystallization. Pikal at 1808.

The sterility of lyophilized products is further ensured by sterile filtration immediately before filling into the final container, coupled with minimal exposure to contaminants during processing. Pikal at 1808; *see also* Rey at 258 ("[S]olutions are sterile filtered, aseptically filled

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into containers, and freeze-dried."); *id.* at 441 ("The ability of running th[e] [lyophilization] process under sterile conditions helps, however, to make it especially attractive to the pharmaceutical industry."). This is particularly important for pharmaceutical products intended for parenteral administration, where sterility is paramount. *See* Rey at 269 ("Since many freeze-dried products tend to be injectable formulations, they are required to be manufactured under sterile conditions."). By reducing exposure to potential contaminants and effectively removing moisture, the lyophilization process ensures that the final product remains sterile and stable over time. *See, e.g.*, Pikal at 1808; Brittain 1999 at 213-14; Kern at 107; Przic at 553; Craig at 198; FDA_7/93.

Furthermore, the '608 Publication further teaches that lyophilized phenobarbital sodium drug compositions can be sterile. Specifically, the '608 Publication discloses that "[d]epending on the desired amount of the lyophilized Phenobarbital Sodium product, the Phenobarbital Sodium solution may be lyophilized in any amount or the solution may be aliquoted into sterile containers (e.g., vials)." '608 Publication at [0079]. By aliquoting the solution into sterile vials prior to lyophilization, the '608 Publication highlights an effective method for producing sterile lyophilized drug products, further supporting the feasibility and practicality of creating sterile phenobarbital sodium compositions.

Given the well-established application of lyophilization in the pharmaceutical industry, a POSA would have recognized that lyophilized phenobarbital sodium drug compositions would be sterile.

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iii. A POSA Would Have Been Motivated and Would Have Had a Reasonable Expectation of Success in Producing a Pharmaceutical Product Comprising Lyophilized Phenobarbital Sodium Compositions Containing at Least 98% Phenobarbital Sodium

A POSA would have been motivated, with a reasonable expectation of success, to produce a pharmaceutical product comprising lyophilized phenobarbital sodium compositions containing at least 98% phenobarbital sodium. As discussed above in Sections VII.A.4 and VII.B.1.b, the prior art and market examples, such as Nobelbar, demonstrate that a lyophilized amorphous phenobarbital sodium composition containing at least 98% phenobarbital sodium is a feasible and practical approach. Nobelbar has been on the market since December 2008 and is known for its efficacy and safety. Kawada 2011 at 209-10. Nobelbar is specifically noted for being "a lyophilized injection composed of ***drug substance only***, without additives," which directly supports the feasibility of achieving a composition with at least 98% lyophilized phenobarbital sodium. Deliberation Results Report at 5 (emphasis added); *see also* Kawada 2011 at 205. The absence of these additives in Nobelbar aligns with the safety and stability requirements for neonatal and pediatric use. Kawada 2011 at 205-06; Kawada 2009 at 660-01. Furthermore, the lyophilized phenobarbital sodium disclosed in the '608 Publication contains "no less than 98% Phenobarbital Sodium" '608 Publication at [0010], [0024], [0071], [0103]-[0104], Table 2-3, 7-13, 16. Once the lyophilized phenobarbital sodium has been reconstituted after storage, the '608 Publication discloses that the reconstituted solution has "no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG," demonstrating its ability to remain storage-stable and essentially void of "toxic" impurities. *Id.* at [0002], [0006], [0024], [0101].

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Given the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the ’608 Publication, a POSA would recognize that it is not only possible but also advantageous to develop a lyophilized amorphous phenobarbital sodium composition containing at least 98% phenobarbital sodium. The practicality, stability, and safety of Nobelbar and compositions disclosed in the ’608 Publication exemplify the benefits of such high-purity formulations, motivating a POSA to pursue this approach with a reasonable expectation of success.

iv. A POSA Would Have Known That 65 mg, 100 mg, 130 mg, and 200 mg Dosages of Phenobarbital Sodium Were Well-Documented in the Pharmaceutical Industry and Already on the Market and Would Have Been Motivated with a Reasonable Expectation of Success to Produce 65 mg, 100 mg, 130 mg, or 200 mg Dosages of Lyophilized Phenobarbital Sodium Drug Products in Single Use Vials

A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 65 mg, 100 mg, 130 mg, or 200 mg in single use vials, leveraging the established efficacy and safety of these dosages in therapeutic applications. As discussed above in Sections VII.A.5 and VII.B.1.b, these specific dosages are well-documented in the pharmaceutical industry. Phenobarbital sodium injection has been available in concentrations of 65 mg/mL and 130 mg/mL with a fill volume of 1 mL, providing precise and effective dosage forms. Hikma at 35 and 62. The ’608 Publication also discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg. ’608 Publication at [0025], [0099]. Additionally, Shah teaches lyophilized phenobarbital sodium compositions present in a concentration of 10-200 mg/mL. Shah at 6:57-64.

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A POSA would have recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 65 mg, 100 mg, 130 mg, or 200 mg is both feasible and supported by existing clinical use.

A POSA would have also been motivated, with a reasonable expectation of success, to provide phenobarbital sodium solutions in a range of concentrations to accommodate individual patient weights. Understanding the need for tailored dosing, a POSA would recognize that different concentrations of phenobarbital sodium solutions, such as 65 mg and 130 mg, would allow for precise dosing based on a patient's weight. Parker describes phenobarbital sodium solutions for injection "in an amount of 15 to 200 mg/mL." Parker at [0017]. Furthermore, the dosage of Nobelbar for intravenous administration is 20 mg/kg, reinforcing the need for precise dosing to match patient weights. *See* Deliberation Results Report at 2. Therefore, a vial containing 65 mg of phenobarbital sodium would be suitable for a neonate with a body weight of about 3.25 kg (approximately 7 pounds), while a vial containing 130 mg would be appropriate for an infant weighing about 6.5 kg (around 14 pounds).

Moreover, the practice of using single use vials for these dosages further supports their viability. *See supra* Section VII.A.5. A POSA would have recognized the benefits that single-dose packaging provides for both patients and healthcare professionals, especially for lyophilized phenobarbital sodium products, as medications intended for parenteral administration are commonly packaged in single-dose vials. *See* Silberzweig at 111 ("Medication from an SDV is intended for parenteral administration for a single patient during a single procedure."). For example, the '608 Publication teaches aliquoting phenobarbital sodium into single use dose vials

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for lyophilization. '608 Publication at [0079] ("[T]o produce 65 mg or 130 mg doses of lyophilized Phenobarbital Sodium, a batch may be dissolved, mixed, pH adjusted if necessary, and filtered and then aliquoted into single use dose vials for lyophilization."). Single use vials, unlike multi-dose packaging, ensure that each dose is sterile and accurately measured, which minimizes the risk of contamination and ensures patient safety by human error in medication dispensing. *See* Silberzweig at 111 ("The preservative agents [found in multiple-dose vials] has no effect on viruses and does not protect against contamination when healthcare personnel fail to follow safe injection practices."); Bawden at 294-97; Mattner at Abstract, 12-14. Furthermore, single use vials allow medical professionals to monitor patient intake and prevent overdoses. This practice aligns with standard medical protocols to maintain sterility and efficacy in injectable medications.

v. A POSA Would Have Known that Phenobarbital Sodium Can Degrade to Produce Harmful Compounds Such as Phenylethylacetylurea (PEAU), 2-Ethyl-2-phenylmalonamide (2EPMM), and Alpha-phenylbutyrylguanidine (PBG)

A POSA would have recognized that phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation. *See supra* Sections VII.A.1-2, VII.B.1.a.iv. Phenobarbital sodium was known to be "very soluble in water." USP at 2493; *see also* USP at 5665-66; West-Ward at § 9. This high solubility means that phenobarbital sodium dissolves readily, which can increase the rate of degradation in aqueous solutions. Deliberation Results Report at 4; *see also* USP at 2493. The degradation of phenobarbital sodium in the presence of water, bases, oxidation, and heat presents challenges in formulation development, particularly for injectable forms where stability is important. Parker at [0007]; Deliberation Results Report at 4. Phenobarbital sodium's susceptibility to hydrolysis in the presence of

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hydroxyl ions from water leads to the destruction of the phenobarbital ring complex, resulting in the formation of "harmful" degradation products such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). Parker at [0004], [0006], [0007], Table 1; *see also* Tishler at Abstract, 214 (disclosing PEAU as a degradant of phenobarbital).

Shah also discloses that "[o]ne of the problems associated with a phenobarbital composition . . . is its instability due to hydrolysis, which causes it to possess a higher level of impurities. While the compound is freely soluble in water, with solubility reported to be as high as 333 mg/ml to 1 g/ml, the presence of hydroxyl ions from the water in the composition results in a hydrolysis pathway that can destroy the phenobarbital ring complex. This destruction results in the possible formation of impurities including harmful degradants or precipitates." Shah at 1:33-42. Shah then identifies 2-phenyl-2-ethyl acetyl urea (PEAU), 2-phenyl-2-ethyl-malonamide (2EPMM), and α-phenylbutyrylguanidine (PBG) as potential impurities present from the API or generated by the degradation of phenobarbital sodium during the manufacturing or stability of the pharmaceutical compositions. *Id.* at 5:32-40, 6:47-50, cl. 4.

The '608 Publication further teaches that "in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) . . . [that] are toxic and cause severe side effects." '608 Publication at [0006]. The '608 Publication reports that "PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts

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both calcium and folate metabolism. . . . Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate." *Id.* at [0006].

Regulatory guidelines and industry standards emphasize the need to control impurities in pharmaceutical formulations to ensure the safety of APIs. *See supra* Sections VII.A.2, VII.B.1.a.iv. For example, the EMEA Guideline, ICH Q3A(R2), and ICH Q3B(R2) stress the importance of identifying and controlling actual and potential impurities that may arise during synthesis, purification, and storage. EMEA Guideline at 4; ICH Q3A(R2) at § 3; ICH Q3B(R2) at § 2. In the context of phenobarbital sodium, the degradation products PEAU, 2EPMM, and PBG are well-documented, highlighting the necessity of stringent impurity control. Parker at [0004], [0006], [0007], Table 1.

To address the issue of degradation, strategies to minimize the presence of impurities include the use of stable formulations that prevent the formation of significant amounts of degradation products during storage. *See* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. Parker, for instance, provides formulations that include phenobarbital sodium combined with a C1-C4 alcohol, such as ethanol, and a glycol, with a pH between 9 and 12, preferably from 9.2 to 10.2. *Id.* at Abstract, [0017], [0034], [0036], [0039], cls. 1-4. These formulations are designed to be extremely stable and do not generate significant amounts of impurities during extended storage. *Id.* at Abstract, [0017].

The presence of impurities such as PEAU, 2EPMM, and PBG, even in minimal amounts, underscores the need for rigorous impurity control in phenobarbital sodium formulations. The prior art demonstrates that maintaining low moisture content is important to minimizing these impurities. *Id.* at Abstract, [0017]. For example, Parker's stable phenobarbital sodium solutions contain no more than 0.8% PEAU impurity after two years of storage at room temperature, and

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no detectable amount of PBG impurity after the same period. *Id.* at [0017], cls. 1, 6. This highlights the importance of formulation strategies that focus on controlling moisture content and other factors that contribute to degradation.

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

vi. A POSA Would Have Recognized that Lyophilized Phenobarbital Sodium Drug Products Stored at Room Temperature for 6 Months Would Form No More Than 0.1% PEAU When Reconstituted with 10 mL of an Aqueous Solution

As detailed above in Sections VII.A.2 and VII.B.1.a.iv-v, a POSA would have recognized that phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in the formation of degradation products such as PEAU. A POSA would have known PEAU as a potential "harmful" degradant of phenobarbital sodium and would be motivated to employ strategies to minimize such impurity when a lyophilized phenobarbital sodium drug product is reconstituted in an aqueous solution. *See* Parker at [0004], [0006], [0007], Table 1; *see also* Shah at 1:33-42 ("This destruction [of the phenobarbital ring complex] results in the possible formation of impurities including harmful degradants or precipitates.").

Stability testing, commonly performed to assess the degradation profile of pharmaceutical products, would be routine to this process. *See* supra Sections VII.A.4. Nobelbar, for instance, reported "no clear changes were observed in any of the test items" when the

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stability of the formulation was evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. These stability studies confirm the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation.

Shah also provides that "[o]ne known method of improving the stability of phenobarbital sodium involves the use of a lower pH and the use of a mixture of water and generic solvents such as alcohol, propylene glycol, glycerin, benzyl alcohol, or polyethylene glycol." Shah at 1:43-46. Shah further teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2.

Furthermore, the '608 Publication discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water, demonstrating methods to decrease the formation of these toxic degradation products. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches compositions of, methods of producing, and use of a lyophilized amorphous phenobarbital sodium formulation with high storage stability and purity. *Id.* at [0010]. Such methods include "adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution." *Id.* at [0013]. To adjust the pH of the phenobarbital sodium solution, the '608 Publication suggests using hydrochloric acid (HCl) or Sodium Hydroxide (NaOH). *Id.* at [0077]. The '608 Publication also notes that "[i]n preferred

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embodiments, the Water for Injection is sparged with nitrogen [for at least 30 minutes] prior to adding the Phenobarbital Sodium" and "[i]n additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium." *Id.* at [0014]. The '608 Publication further discloses filtering the phenobarbital sodium solution prior to lyophilization. *Id.* at [0018]. The lyophilized phenobarbital sodium disclosed in the '608 Publication can be reconstituted in "either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration." *Id.* at [0101]. The '608 Publication also teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119].

The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. Once the lyophilized phenobarbital sodium has been reconstituted after storage "for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC)," the '608 Publication discloses that the reconstituted solution forms "no more than 0.1% phenylethylacetylurea (PEAU)." *Id.* at [0016], [0088].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would have recognized that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.1% PEAU when reconstituted in 10 mL of an aqueous solution upon storage over six months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized

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amorphous phenobarbital sodium composition. The strategies employed to control moisture content and maintain the stability of the drug product would ensure that the formation of harmful degradation products is minimized.

Consequently, based on the prior art and known understanding of common lyophilization techniques, a POSA would have been motivated to pursue, with a reasonable expectation of success, a storage stable pharmaceutical product containing a lyophilized and sterile composition comprising a 65 mg, 100 mg, 130 mg, or 200 mg dose of no less than 98% phenobarbital sodium in a single use dose vial.

By way of a non-limiting, illustrative example, claim 1 of the ’076 Patent is obvious over the ’608 Publication in light of the general knowledge of the skilled artisan. It is also obvious over the ’608 Publication in view of one or more of Nobelbar (as evidenced by Deliberation Results Report, Kawada 2009, Kawada 2011, Nobelbar Label, and any other information about Nobelbar gained during discovery), Gardenal (as evidenced by Bertaux and Fournier and any other information about Gardenal gained during discovery), Shah, Kern, Sznitowska (collectively, **Group 1 references**) in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references (e.g., the ’608 Publication, Nobelbar, Gardenal, Shah, Kern, and/or Sznitowska) in view of Hikma (as evidenced by any other information about the phenobarbital sodium injection disclosed in Hikma gained during discovery) in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references in view of one or more of Rey, Pikal, Brittain 1999, Przic, Craig, and/or FDA_7/93 (collectively, **Group 2 references**), in light of the general knowledge of the skilled artisan.

Based on the lyophilized phenobarbital sodium compositions described in the ’608 Publication, a POSA would have been motivated, with a reasonable expectation of success, to

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produce a storage stable pharmaceutical product containing a lyophilized and sterile composition comprising a 65 mg, 100 mg, 130 mg, or 200 mg dose of no less than 98% phenobarbital sodium in a single use dose vial. A POSA would have also been motivated and expected to produce such a storage stable pharmaceutical product containing lyophilized phenobarbital sodium composition containing no less than 98% phenobarbital sodium, based on the lyophilized phenobarbital sodium drug products that were tested as model drugs and already on the market described in the **Group 1 references.** A POSA would have also known and thus would have been motivated, with a reasonable expectation of success, to produce 65 mg, 100 mg, 130 mg, or 200 mg dosages of lyophilized phenobarbital sodium drug products in single use vials as a result of their general knowledge. This motivation and reasonable expectation of success are supported by the disclosures of Hikma. A POSA would have also recognized and thus would have been motivated, with a reasonable expectation of success, to produce lyophilized phenobarbital sodium drug compositions that is sterile as a result of their general knowledge. This motivation and reasonable expectation of success are supported by the disclosures of **Group 2 references**.

Furthermore, a POSA would have been motivated to pursue, with a reasonable expectation of success, a pharmaceutical product containing a lyophilized and sterile composition comprising a 65 mg, 100 mg, 130 mg, or 200 mg dose of no less than 98% phenobarbital sodium in a single use dose vial, wherein the composition has the property that when stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).

By way of a non-limiting, illustrative example, claim 7 of the ’076 Patent is obvious over the ’608 Publication in light of the general knowledge of the skilled artisan. It is also obvious

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over the ’608 Publication in view of Nobelbar (as evidenced by Deliberation Results Report, Kawada 2009, and Kawada 2011, Nobelbar Label, and any other information about Nobelbar gained during discovery), Gardenal (as evidenced by Bertaux and Fournier and any other information about Gardenal gained during discovery), Shah, Kern, and/or Sznitowska (collectively, **Group 1 references**) in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references (e.g., the ’608 Publication, Nobelbar, Gardenal, Shah, Kern, and/or Sznitowska) in view of Hikma (as evidenced by any other information about the phenobarbital sodium injection disclosed in Hikma gained during discovery), Silberzweig, Bawden, and/or Mattner (collectively, **Group 2 references)** in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references in view of one or more of Rey, Pikal, Brittain 1999, Przic, Craig, and/or FDA_7/93 (collectively, **Group 3 references**), in light of the general knowledge of the skilled artisan. It is also obvious over one or more of these references in view of one or more of Parker, Tishler, USP, and/or West-Ward (collectively, **Group 4 references**). It is also obvious over one or more of these references further in view of one or more of EMEA Guideline, ICH Q3A(R2), ICH Q3B(R2), Anderson 2000, Anderson 2012, Alsante, Liu, and/or Prabu (collectively, **Group 5 references**).

Based on the lyophilized phenobarbital sodium compositions described in the ’608 Publication, a POSA would have been motivated, with a reasonable expectation of success, to produce a pharmaceutical product containing a lyophilized and sterile composition comprising a 65 mg, 100 mg, 130 mg, or 200 mg dose of no less than 98% phenobarbital sodium in a single use dose vial, wherein the composition has the property that when stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution, the reconstituted composition contains no more than 0.1% PEAU. A POSA would have also been

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motivated and expected to produce such a pharmaceutical product containing lyophilized phenobarbital sodium composition containing no less than 98% phenobarbital sodium, based on the lyophilized phenobarbital sodium drug products that were tested as model drugs and already on the market described in the **Group 1 references.** A POSA would have also known and thus would have been motivated, with a reasonable expectation of success, to produce 65 mg, 100 mg, 130 mg, or 200 mg dosages of lyophilized phenobarbital sodium drug products in single use vials as a result of their general knowledge. This motivation and reasonable expectation of success are supported by the disclosures of **Group 2 references**. A POSA would have also recognized and thus would have been motivated, with a reasonable expectation of success, to produce lyophilized phenobarbital sodium drug compositions that is sterile as a result of their general knowledge. This motivation and reasonable expectation of success are supported by the disclosures of **Group 3 references**. A POSA would have also expected the drug product, upon reconstitution with 10 mL of an aqueous solution after six months of storage at room temperature, to form no more than 0.1% PEAU for the reasons already discussed in Sections VII.A and VII.B.2.a.v-vi. The POSA would have known and thus would have been motivated to reduce PEAU, with a reasonable expectation of success, as a result of their general knowledge. This motivation and reasonable expectation of success would be supported by **Group 4 references**. This motivation is further supported by the **Group 5 references**.

b. Obviousness of the Dependent Claims

The state of the art from Section VII.A, the scope and content of the prior art from Section VI, and the analyses presented for claims 1 and 7 of the ’076 Patent from Section VII.B.2.a (as well as the analyses presented for claims of the ’598 Patent from Section VII.B.1)

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are incorporated herein. Sun also presents the following analysis specific to the dependent claims of the ’076 Patent.

Claim 2 of the ’076 Patent depends from claim 1 and further requires the composition to have the property to contain, upon storage for six months at 40° C, no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 2. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PEAU. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU in the final product.

The ’608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, ’608 Publication at Abstract, [0002]. The ’608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5%

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Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. Once the lyophilized phenobarbital sodium has been reconstituted after storage "for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC)," the '608 Publication discloses that the reconstituted solution forms "no more than 0.1% phenylethylacetylurea (PEAU)." *Id.* at [0016], [0088]. The '608 Publication notes that the accelerated stability conditions are 40° C, 75% RH. *Id.* at [0013], [0016], [0103], Tables 2-3, 10-13, 16.

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.1% PEAU when reconstituted for injection with 10 mL of an aqueous solution upon storage for six months at 40° C and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 2 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a.

Claim 3 of the '076 Patent depends from claim 1 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted for injection with 10 mL of an aqueous solution. '076 Patent at cl. 3. As discussed above in Sections VII.A.2 and VII.B.2.a.v,

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phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PEAU. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608

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Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.)." *Id.* at [0016]; *see also id.* at [0024], [0071], [0089], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% PEAU when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 3 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a.

Claim 4 of the '076 Patent depends from claim 1 and further requires the composition to have the property to contain, upon storage at 40° C. for 6 months, no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted for injection with 10 mL of an aqueous solution. '076 Patent at cl. 4. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation

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products such as 2EPMM and PBG. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of 2EPMM and PBG in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at

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RT and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101]. The '608 Publication notes that the accelerated stability conditions are 40° C, 75% RH. *Id.* at [0013], [0016], [0103], Tables 2-3, 10-13, 16.

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of 2EPMM or PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at 40° C. for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 4 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a.

Claim 5 of the '076 Patent depends from claim 1 and further requires the composition to be amorphous. '076 Patent at cl. 5. As discussed above in Sections VII.A.3 and VII.B.1.a.iii, a POSA would have recognized that lyophilization was a common technique to alter the physical form, chemical stability, and dissolution characteristics of pharmaceutical products, making it a preferred method for enhancing the performance of various drugs. Brittain 1999 at 214. Specifically, lyophilization is employed to convert crystalline materials to amorphous forms by preventing the formation of crystalline structures during the rapid freezing process. Brittain 1999 at 214-15; Bernstein at 254; Craig at 180; *see also* Haleblian at 1273; Einfalt at 308-309; Yu at Abstract, 29. The amorphous form of a drug often enhances its dissolution rate and

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bioavailability, making it a preferred form for certain pharmaceutical applications (e.g., drugs that must be reconstituted). Craig at 180; Haleblian at 1273-74; Einfalt at 305, 307; Yu at 27. Furthermore, prior art provides numerous examples of successful applications of lyophilization to produce amorphous pharmaceuticals, including lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7. A POSA would have known that using the lyophilization process would produce a storage-stable form of lyophilized *amorphous* phenobarbital sodium composition.

Furthermore, the '608 Publication discloses "[a] composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium." '608 Publication at Abstract; *see also id.* at [0010]-[0011], [0081]. The '608 Publication also notes that "Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.)." *Id.* at [0012].

A POSA, equipped with the extensive knowledge from the prior art, would have been motivated and would have had a reasonable expectation of success in using lyophilization to produce lyophilized amorphous phenobarbital sodium composition. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms would guide a POSA in developing a stable and effective lyophilized phenobarbital sodium composition. Thus, claim 5 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a, optionally further in view of Bernstein, Einfalt, Yu, and/or Haleblian.

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Claim 6 of the ’076 Patent depends from claim 1 and further requires the composition to have the property to contain, upon storage at room temperature for 24 months, at most 0.1% phenylethylacetylurea (PEAU) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 6. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PEAU. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that “the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU] present following 36 months of storage at 20-25° C. does not exceed 0.2%.” Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU in the final product.

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The ’608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, ’608 Publication at Abstract, [0002]. The ’608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the ’608 Publication “do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073]. Once the lyophilized phenobarbital sodium has been reconstituted after storage “for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC),” the ’608 Publication discloses that the reconstituted solution forms “no more than 0.1% phenylethylacetylurea (PEAU).” *Id.* at [0016], [0088]. The ’608 Publication notes that “at least 6 months under accelerated stability conditions which is equivalent to 24 months at [room temperature].” *Id.* at [0017], [0071], [0091], [0101].

A POSA would also understand the importance of shelf life stability, recognizing that stability testing is important “to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors” and to establish appropriate shelf life and storage conditions. FDA Guidance for Industry Q1A(R2) at 2. Manufacturers often carry out ongoing stability studies, using appropriate statistical methods to monitor and confirm stability predictions, and may extend the shelf life of the API or finished product through limited extrapolation of real-time data if justified. *See* FDA Guidance for Industry Q1A(R2) at 7, 15-16; Annex 10 at 320-21, 334-35.

Given the extensive knowledge of phenobarbital sodium’s degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital

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sodium disclosed in the ’608 Publication and Shah and the importance of shelf life stability, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form at most 0.1% PEAU when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 24 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 6 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a, optionally further in view of FDA Guidance for Industry and/or Annex 10.

Claim 8 of the ’076 Patent depends from claim 7 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 8. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PEAU. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark,

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6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.)." *Id.* at [0016]; *see also id.* at [0024], [0071], [0089], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized

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phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% PEAU when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 8 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 9 of the ’076 Patent depends from claim 7 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 9. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as 2EPMM. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that “the present disclosure relates to

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a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including 2EPMM] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of 2EPMM in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized

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phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of 2EPMM when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 9 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 10 of the ’076 Patent depends from claim 7 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of alpha-phenylbutyrylguanidine (PBG) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 10. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PBG. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that “the present disclosure relates to

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a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PBG] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PBG in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized

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phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 10 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 11 of the ’076 Patent depends from claim 10 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 11. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as 2EPMM. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported “no clear changes” in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that “the present

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disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including 2EPMM] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of 2EPMM in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would further recognize that

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lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of 2EPMM when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 11 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 12 of the ’076 Patent depends from claim 7 and further requires the composition to be amorphous. ’076 Patent at cl. 12. As discussed above in Sections VII.A.3 and VII.B.1.a.iii, a POSA would have recognized that lyophilization was a common technique to alter the physical form, chemical stability, and dissolution characteristics of pharmaceutical products, making it a preferred method for enhancing the performance of various drugs. Brittain 1999 at 214. Specifically, lyophilization is employed to convert crystalline materials to amorphous forms by preventing the formation of crystalline structures during the rapid freezing process. Brittain 1999 at 214-15; Bernstein at 254; Craig at 180; *see also* Haleblian at 1273; Einfalt at 308-309; Yu at Abstract, 29. The amorphous form of a drug often enhances its dissolution rate and bioavailability, making it a preferred form for certain pharmaceutical applications. Craig at 180; Haleblian at 1273-74; Einfalt at 305, 307; Yu at 27. Furthermore, prior art provides numerous examples of successful applications of lyophilization to produce amorphous pharmaceuticals, including lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7. A POSA would have known that using the lyophilization process would produce a storage-stable form of lyophilized *amorphous* phenobarbital sodium composition.

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Furthermore, the ’608 Publication discloses “[a] composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium.” ’608 Publication at Abstract; *see also id.* at [0010]-[0011], [0081]. The ’608 Publication also notes that “Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012].

A POSA, equipped with the extensive knowledge from the prior art, would have been motivated and would have had a reasonable expectation of success in using lyophilization to produce lyophilized amorphous phenobarbital sodium composition. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms would guide a POSA in developing a stable and effective lyophilized phenobarbital sodium composition. Thus, claim 12 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a, optionally further in view of Bernstein, Einfalt, Yu, and/or Haleblian.

Claim 13 of the ’076 Patent depends from claim 12 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of alpha-phenylbutyrylguanidine (PBG) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 13. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PBG. Strategies to

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control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PBG] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PBG in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608

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Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 13 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 14 of the '076 Patent depends from claim 1 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% phenylethylacetylurea (PEAU) and no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted for injection with 10 mL of an aqueous solution. '076 Patent at cl. 14. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is

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susceptible to degradation, resulting in harmful degradation products such as PEAU, 2EPMNN, and PBG. Strategies to control moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU, 2EPMM, and PBG] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PEAU, 2EPMM, and PBG in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608

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Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608 Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% PEAU and no more than 0.05% of 2EPMM or PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 14 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a.

Claim 15 of the '076 Patent depends from claim 14 and further requires the composition to be amorphous. '076 Patent at cl. 15. As discussed above in Sections VII.A.3 and VII.B.1.a.iii, a POSA would have recognized that lyophilization was a common technique to alter the physical form, chemical stability, and dissolution characteristics of pharmaceutical products, making it a

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preferred method for enhancing the performance of various drugs. Brittain 1999 at 214. Specifically, lyophilization is employed to convert crystalline materials to amorphous forms by preventing the formation of crystalline structures during the rapid freezing process. Brittain 1999 at 214-15; Bernstein at 254; Craig at 180; *see also* Haleblian at 1273; Einfalt at 308-309; Yu at Abstract, 29. The amorphous form of a drug often enhances its dissolution rate and bioavailability, making it a preferred form for certain pharmaceutical applications. Craig at 180; Haleblian at 1273-74; Einfalt at 305, 307; Yu at 27. Furthermore, prior art provides numerous examples of successful applications of lyophilization to produce amorphous pharmaceuticals, including lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7. A POSA would have known that using the lyophilization process would produce a storage-stable form of lyophilized *amorphous* phenobarbital sodium composition.

Furthermore, the ’608 Publication discloses “[a] composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium.” ’608 Publication at Abstract; *see also id.* at [0010]-[0011], [0081]. The ’608 Publication also notes that “Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012].

A POSA, equipped with the extensive knowledge from the prior art, would have been motivated and would have had a reasonable expectation of success in using lyophilization to produce lyophilized amorphous phenobarbital sodium composition. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms would

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guide a POSA in developing a stable and effective lyophilized phenobarbital sodium composition. Thus, claim 15 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a, optionally further in view of Bernstein, Einfalt, Yu, and/or Haleblian.

Claim 16 of the ’076 Patent depends from claim 1 and further requires the product to comprise a 100 mg dose in the single use dose vial. ’076 Patent at cl. 16. A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 100 mg in single use vials, leveraging the established efficacy and safety of these dosages in therapeutic applications. As discussed above in Section VII.B.2.a.iv, a 100 mg dose is well-documented in the pharmaceutical industry. The ’608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg. ’608 Publication at [0025], [0099]. Shah also discloses lyophilized phenobarbital sodium compositions in a concentration of 10-200 mg/mL, including 100 mg/mL. Shah at 6:57-64. A POSA would have recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 100 mg is both feasible and supported by existing clinical use. Thus, claim 16 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 1 in Section VII.B.2.a.

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Claim 17 of the ’076 Patent depends from claim 7 and further requires the product to comprise a 100 mg dose in the single use dose vial. ’076 Patent at cl. 17. A POSA would have been motivated with a reasonable expectation of success to produce lyophilized phenobarbital sodium solutions in amounts of about 100 mg in single use vials, leveraging the established efficacy and safety of these dosages in therapeutic applications. As discussed above in Section VII.B.2.a.iv, a 100 mg dose is well-documented in the pharmaceutical industry. The ’608 Publication discloses lyophilized phenobarbital sodium compositions in doses of 65 mg, 100 mg, 130 mg, and 200 mg. ’608 Publication at [0025], [0099]. Shah also discloses lyophilized phenobarbital sodium compositions in a concentration of 10-200 mg/mL, including 100 mg/mL. Shah at 6:57-64. A POSA would have recognized that using these well-accepted dosages would minimize risks and uncertainties associated with formulation development, as their efficacy and safety profiles are already known. Furthermore, the prior art demonstrates that producing lyophilized phenobarbital sodium solutions in amounts of about 100 mg is both feasible and supported by existing clinical use. Thus, claim 17 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 18 of the ’076 Patent depends from claim 8 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) when reconstituted for injection with 10 mL of an aqueous solution. ’076 Patent at cl. 18. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as 2EPMM. Strategies to control

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moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including 2EPMM] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of 2EPMM in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608

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Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of 2EPMM when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 18 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 19 of the '076 Patent depends from claim 8 and further requires the composition to have the property to contain, upon storage at room temperature for 6 months, no more than 0.05% of alpha-phenylbutyrylguanidine (PBG) when reconstituted for injection with 10 mL of an aqueous solution. '076 Patent at cl. 19. As discussed above in Sections VII.A.2 and VII.B.2.a.v, phenobarbital sodium, due to its high solubility in water and hygroscopic nature, is susceptible to degradation, resulting in harmful degradation products such as PBG. Strategies to control

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moisture content and maintain the stability of the drug product are well-documented in the prior art, ensuring that the formation of harmful degradation products is minimized. *See supra* Sections VII.A.2-4, VII.B.2.a.ii, VII.B.2.a.v-vi; *see also* Anderson 2000 at 262; Anderson 2012 at 384-85, 389; Alsante at 237, 239; Liu; Prabu at 68-69. A POSA would have been motivated to employ strategies to minimize such impurities in lyophilized phenobarbital sodium drug products. Nobelbar reported "no clear changes" in stability when evaluated by long-term storage tests (25 ± 2°C/60 ± 5% RH, in the dark, 36 months), accelerated tests (40 ± 2°C/75 ± 5% RH, in the dark, 6 months), and caustic tests (50 ± 2°C, 3 months), as well as light and relative acceleration studies. Deliberation Results Report at 5. Shah also teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PBG] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. These tests confirmed the reliability and effectiveness of lyophilization in producing a stable product with minimal degradation, demonstrating the practicality of achieving low levels of PBG in the final product.

The '608 Publication further discloses storage stable lyophilized compositions of phenobarbital sodium salt having high purity that are essentially void of impurities upon reconstitution in water. *E.g.*, '608 Publication at Abstract, [0002]. The '608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose. *Id.* at [0119]. The lyophilized phenobarbital sodium compositions disclosed in the '608 Publication "do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG." *Id.* at [0073]. The '608

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Publication further discloses that "the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101].

Given the extensive knowledge of phenobarbital sodium's degradation pathways and the documented success of stable formulations like Nobelbar and the lyophilized phenobarbital sodium disclosed in the '608 Publication and Shah, a POSA would recognize that lyophilized phenobarbital sodium drug products, using known lyophilization parameters and production methods, would form no more than 0.05% of PBG when reconstituted for injection with 10 mL of an aqueous solution upon storage at room temperature for 6 months and would have been motivated, with a reasonable expectation of success, to produce such storage-stable forms of lyophilized amorphous phenobarbital sodium composition. Thus, claim 19 is obvious over the scope and content of prior art discussed in Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a.

Claim 20 of the '076 Patent depends from claim 8 and further requires the composition to be amorphous. '076 Patent at cl. 20. As discussed above in Sections VII.A.3 and VII.B.1.a.iii, a POSA would have recognized that lyophilization was a common technique to alter the physical form, chemical stability, and dissolution characteristics of pharmaceutical products, making it a preferred method for enhancing the performance of various drugs. Brittain 1999 at 214. Specifically, lyophilization is employed to convert crystalline materials to amorphous forms by

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preventing the formation of crystalline structures during the rapid freezing process. Brittain 1999 at 214-15; Bernstein at 254; Craig at 180; *see also* Haleblian at 1273; Einfalt at 308-309; Yu at Abstract, 29. The amorphous form of a drug often enhances its dissolution rate and bioavailability, making it a preferred form for certain pharmaceutical applications. Craig at 180; Haleblian at 1273-74; Einfalt at 305, 307; Yu at 27. Furthermore, prior art provides numerous examples of successful applications of lyophilization to produce amorphous pharmaceuticals, including lactose, raffinose, and aspirin. Brittain 1999 at 215, Table 7. A POSA would have known that using the lyophilization process would produce a storage-stable form of lyophilized *amorphous* phenobarbital sodium composition.

Furthermore, the ’608 Publication discloses “[a] composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium.” ’608 Publication at Abstract; *see also id.* at [0010]-[0011], [0081]. The ’608 Publication also notes that “Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).” *Id.* at [0012].

A POSA, equipped with the extensive knowledge from the prior art, would have been motivated and would have had a reasonable expectation of success in using lyophilization to produce lyophilized amorphous phenobarbital sodium composition. The well-documented effectiveness of lyophilization in converting crystalline materials to amorphous forms would guide a POSA in developing a stable and effective lyophilized phenobarbital sodium composition. Thus, claim 20 is obvious over the scope and content of prior art discussed in

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Sections VI and VII.A, in view of common knowledge in the art. It is also obvious over each of the exemplary combinations presented above for claim 7 in Section VII.B.2.a, optionally further in view of Bernstein, Einfalt, Yu, and/or Haleblian.

c. Identification of Prior Art

The tables below list prior art that anticipates and/or renders obvious one or more of claims 1-20 of the ’076 Patent. The attached claim charts in Exhibits B-1 to B-9 demonstrate where each limitation of the claims is found in, either expressly or inherently in the larger context of the passage, or rendered obvious by, certain of the references listed below, as understood by a person having ordinary skill in the art. The following patents, publications, products and/or services are prior art under at least 35 U.S.C. §§ 102(a), (b) or (d).

i. Prior Art References, Patents, Patent Publications, and Non-Patent Publications to the Claims 1-20 of the ’076 Patent

Chart	Reference	Filing Date	Date of Issue or Publication	Citation	Claims
B-1	U.S. Publication No. 2021/0085608 A1	September 18, 2020	March 25, 2021	the ’608 Publication	Anticipated: 1-20 Obvious: 1-20
B-2	Nobelbar		2008	Nobelbar	Anticipated: 1-20 Obvious: 1-20
B-3	Gardenal		As early as 1992	Gardenal	Anticipated: 1-20 Obvious: 1-20
B-4	Joseph Herschel Kern, *Freeze Drying as a Method of Processing Some Pharmaceutical Products* (1954) (dissertation for Doctor of Philosophy, Ohio State University)		1954	Kern	Obvious: 1-20
B-5	Małgorzata Sznitowska et al.,		2009	Sznitowska	Anticipated: 1-20 Obvious: 1-20

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Chart	Reference	Filing Date	Date of Issue or Publication	Citation	Claims
	The physical characteristics of lyophilized tablets containing a model drug in different chemical forms and concentrations, 62(1) ACTA POLONIAE PHARM. 25 (2009)				
B-6	U.S. Patent No. 11,857,683	April 7, 2022	January 2, 2024	Shah	Anticipated: 1-20 Obvious: 1-20
B-7	U.S. Patent Application Publication No. US 2017/0143719	Nov. 18, 2016	May 25, 2017	Parker	Obvious: 1-20
B-8	*2018 Injectable Product Catalog*, HIKMA (2018)		2018	Hikma	Obvious: 1-20

ii. Prior Art Pharmaceutical Compositions/Products To The Claims 1-20 of the '076 Patent

Sun further identifies the commercial embodiments of the inventions described in Exhibits B-1 to B-8, to the extent those pharmaceutical compositions or products were on sale or in public use before the priority date of the '076 Patent. Moreover, on information and belief, Nobelpharma Co., Ltd. ("Nobelpharma") and other companies sold, offered for sale, and/or publicly used products incorporating Nobelpharma's Nobelbar ("Nobelbar") that constitutes prior art to the '076 Patent. Chart B-2 demonstrates where each limitation of the claims is found in Nobelbar. Sun plans to pursue additional information concerning this product during discovery and reserves the right to rely upon any additional information obtained.

Moreover, on information and belief, companies sold, offered for sale, and/or publicly used products incorporating Gardenal that constitutes prior art to the '076 Patent. Chart B-3 demonstrates where each limitation of the claims is found in Gardenal. Sun plans to pursue

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additional information concerning this product during discovery and reserves the right to rely upon any additional information obtained.

iii. Obviousness Combinations

A person having ordinary skill in the art would have been motivated to modify or combine the references described in attached Exhibits B-1 to B-8 as listed below, or further as shown in the exemplary omnibus reference Exhibit B-9, and for the reasons described below.

Reference	In Combination With	Claims
the ’608 Publication	Nobelbar	1-20
	Gardenal	1-20
	Kern	1-20
	Sznitowska	1-20
	Shah	1-20
	Parker	1-20
	Hikma	1-20
Nobelbar	Parker	1-20
	Hikma	1-20
	Parker and Hikma	1-20
	Silberzweig	1-20
	Bawden	1-20
	Mattner	1-20
	Parker and Silberzweig	1-20
	Hikma and Silberzweig	1-20
	Parker and Hikma and Silberzweig	1-20
	Parker and Bawden	1-20
	Hikma and Bawden	1-20
	Parker and Hikma and Bawden	1-20
	Parker and Mattner	1-20
	Hikma and Mattner	1-20
	Parker and Hikma and Mattner	1-20
	Rey	1-20
	Pikal	1-20
	Przic	1-20
	FDA_7/93	1-20
	Parker and Rey	1-20
	Hikma and Rey	1-20
	Parker and Hikma and Rey	1-20
	Parker and Pikal	1-20
	Hikma and Pikal	1-20
	Parker and Hikma and Pikal	1-20
	Parker and Przic	1-20

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Reference	In Combination With	Claims
	Hikma and Przic	1-20
	Parker and Hikma and Przic	1-20
	Parker and FDA_7/93	1-20
	Hikma and FDA_7/93	1-20
	Parker and Hikma and FDA_7/93	1-20
	Bernstein	1-20
	Einfalt	1-20
	Yu	1-20
	Parker and Bernstein	1-20
	Hikma and Bernstein	1-20
	Parker and Hikma and Bernstein	1-20
	Parker and Einfalt	1-20
	Hikma and Einfalt	1-20
	Parker and Hikma and Einfalt	1-20
	Parker and Yu	1-20
	Hikma and Yu	1-20
	Parker and Hikma and Yu	1-20
	EMEA Guideline	1-20
	ICH Q3A(R2)	1-20
	ICH Q3B(R2)	1-20
	Anderson 2000	1-20
	Anderson 2012	1-20
	Liu	1-20
	Prabu	1-20
	Parker and EMEA Guideline	1-20
	Hikma and EMEA Guideline	1-20
	Parker and Hikma and EMEA Guideline	1-20
	Parker and ICH Q3A(R2)	1-20
	Hikma and ICH Q3A(R2)	1-20
	Parker and Hikma and ICH Q3A(R2)	1-20
	Parker and ICH Q3B(R2)	1-20
	Hikma and ICH Q3B(R2)	1-20
	Parker and Hikma and ICH Q3B(R2)	1-20
	Parker and Anderson 2000	1-20
	Hikma and Anderson 2000	1-20
	Parker and Hikma and Anderson 2000	1-20
	Parker and Anderson 2012	1-20
	Hikma and Anderson 2012	1-20
	Parker and Hikma and Anderson 2012	1-20
	Parker and Liu	1-20
	Hikma and Liu	1-20
	Parker and Hikma and Liu	1-20
	Parker and Prabu	1-20
	Hikma and Prabu	1-20
	Parker and Hikma and Prabu	1-20

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Reference	In Combination With	Claims
	Parker	1-20
	Hikma	1-20
	Parker and Hikma	1-20
	Silberzweig	1-20
	Bawden	1-20
	Mattner	1-20
	Parker and Silberzweig	1-20
	Hikma and Silberzweig	1-20
	Parker and Hikma and Silberzweig	1-20
	Parker and Bawden	1-20
	Hikma and Bawden	1-20
	Parker and Hikma and Bawden	1-20
	Parker and Mattner	1-20
	Hikma and Mattner	1-20
	Parker and Hikma and Mattner	1-20
	Rey	1-20
	Pikal	1-20
	Przic	1-20
	FDA_7/93	1-20
	Parker and Rey	1-20
	Hikma and Rey	1-20
	Parker and Hikma and Rey	1-20
Gardenal	Parker and Pikal	1-20
	Hikma and Pikal	1-20
	Parker and Hikma and Pikal	1-20
	Parker and Przic	1-20
	Hikma and Przic	1-20
	Parker and Hikma and Przic	1-20
	Parker and FDA_7/93	1-20
	Hikma and FDA_7/93	1-20
	Parker and Hikma and FDA_7/93	1-20
	Bernstein	1-20
	Einfalt	1-20
	Yu	1-20
	Parker and Bernstein	1-20
	Hikma and Bernstein	1-20
	Parker and Hikma and Bernstein	1-20
	Parker and Einfalt	1-20
	Hikma and Einfalt	1-20
	Parker and Hikma and Einfalt	1-20
	Parker and Yu	1-20
	Hikma and Yu	1-20
	Parker and Hikma and Yu	1-20
	EMEA Guideline	1-20
	ICH Q3A(R2)	1-20

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Reference	In Combination With	Claims
	ICH Q3B(R2)	1-20
	Anderson 2000	1-20
	Anderson 2012	1-20
	Liu	1-20
	Prabu	1-20
	Parker and EMEA Guideline	1-20
	Hikma and EMEA Guideline	1-20
	Parker and Hikma and EMEA Guideline	1-20
	Parker and ICH Q3A(R2)	1-20
	Hikma and ICH Q3A(R2)	1-20
	Parker and Hikma and ICH Q3A(R2)	1-20
	Parker and ICH Q3B(R2)	1-20
	Hikma and ICH Q3B(R2)	1-20
	Parker and Hikma and ICH Q3B(R2)	1-20
	Parker and Anderson 2000	1-20
	Hikma and Anderson 2000	1-20
	Parker and Hikma and Anderson 2000	1-20
	Parker and Anderson 2012	1-20
	Hikma and Anderson 2012	1-20
	Parker and Hikma and Anderson 2012	1-20
	Parker and Liu	1-20
	Hikma and Liu	1-20
	Parker and Hikma and Liu	1-20
	Parker and Prabu	1-20
	Hikma and Prabu	1-20
	Parker and Hikma and Prabu	1-20
Kern	Parker	1-20
	Hikma	1-20
	Parker and Hikma	1-20
	Silberzweig	1-20
	Bawden	1-20
	Mattner	1-20
	Parker and Silberzweig	1-20
	Hikma and Silberzweig	1-20
	Parker and Hikma and Silberzweig	1-20
	Parker and Bawden	1-20
	Hikma and Bawden	1-20
	Parker and Hikma and Bawden	1-20
	Parker and Mattner	1-20
	Hikma and Mattner	1-20
	Parker and Hikma and Mattner	1-20
	Rey	1-20
	Pikal	1-20
	Przic	1-20
	FDA_7/93	1-20

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Reference	In Combination With	Claims
	Parker and Rey	1-20
	Hikma and Rey	1-20
	Parker and Hikma and Rey	1-20
	Parker and Pikal	1-20
	Hikma and Pikal	1-20
	Parker and Hikma and Pikal	1-20
	Parker and Przic	1-20
	Hikma and Przic	1-20
	Parker and Hikma and Przic	1-20
	Parker and FDA_7/93	1-20
	Hikma and FDA_7/93	1-20
	Parker and Hikma and FDA_7/93	1-20
	Bernstein	1-20
	Einfalt	1-20
	Yu	1-20
	Parker and Bernstein	1-20
	Hikma and Bernstein	1-20
	Parker and Hikma and Bernstein	1-20
	Parker and Einfalt	1-20
	Hikma and Einfalt	1-20
	Parker and Hikma and Einfalt	1-20
	Parker and Yu	1-20
	Hikma and Yu	1-20
	Parker and Hikma and Yu	1-20
	EMEA Guideline	1-20
	ICH Q3A(R2)	1-20
	ICH Q3B(R2)	1-20
	Anderson 2000	1-20
	Anderson 2012	1-20
	Liu	1-20
	Prabu	1-20
	Parker and EMEA Guideline	1-20
	Hikma and EMEA Guideline	1-20
	Parker and Hikma and EMEA Guideline	1-20
	Parker and ICH Q3A(R2)	1-20
	Hikma and ICH Q3A(R2)	1-20
	Parker and Hikma and ICH Q3A(R2)	1-20
	Parker and ICH Q3B(R2)	1-20
	Hikma and ICH Q3B(R2)	1-20
	Parker and Hikma and ICH Q3B(R2)	1-20
	Parker and Anderson 2000	1-20
	Hikma and Anderson 2000	1-20
	Parker and Hikma and Anderson 2000	1-20
	Parker and Anderson 2012	1-20
	Hikma and Anderson 2012	1-20

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Reference	In Combination With	Claims
	Parker and Hikma and Anderson 2012	1-20
	Parker and Liu	1-20
	Hikma and Liu	1-20
	Parker and Hikma and Liu	1-20
	Parker and Prabu	1-20
	Hikma and Prabu	1-20
	Parker and Hikma and Prabu	1-20
Sznitowska	Parker	1-20
	Hikma	1-20
	Parker and Hikma	1-20
	Silberzweig	1-20
	Bawden	1-20
	Mattner	1-20
	Parker and Silberzweig	1-20
	Hikma and Silberzweig	1-20
	Parker and Hikma and Silberzweig	1-20
	Parker and Bawden	1-20
	Hikma and Bawden	1-20
	Parker and Hikma and Bawden	1-20
	Parker and Mattner	1-20
	Hikma and Mattner	1-20
	Parker and Hikma and Mattner	1-20
	Rey	1-20
	Pikal	1-20
	Przic	1-20
	FDA_7/93	1-20
	Parker and Rey	1-20
	Hikma and Rey	1-20
	Parker and Hikma and Rey	1-20
	Parker and Pikal	1-20
	Hikma and Pikal	1-20
	Parker and Hikma and Pikal	1-20
	Parker and Przic	1-20
	Hikma and Przic	1-20
	Parker and Hikma and Przic	1-20
	Parker and FDA_7/93	1-20
	Hikma and FDA_7/93	1-20
	Parker and Hikma and FDA_7/93	1-20
	Bernstein	1-20
	Einfalt	1-20
	Yu	1-20
	Parker and Bernstein	1-20
	Hikma and Bernstein	1-20
	Parker and Hikma and Bernstein	1-20
	Parker and Einfalt	1-20

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Reference	In Combination With	Claims
	Hikma and Einfalt	1-20
	Parker and Hikma and Einfalt	1-20
	Parker and Yu	1-20
	Hikma and Yu	1-20
	Parker and Hikma and Yu	1-20
	EMEA Guideline	1-20
	ICH Q3A(R2)	1-20
	ICH Q3B(R2)	1-20
	Anderson 2000	1-20
	Anderson 2012	1-20
	Liu	1-20
	Prabu	1-20
	Parker and EMEA Guideline	1-20
	Hikma and EMEA Guideline	1-20
	Parker and Hikma and EMEA Guideline	1-20
	Parker and ICH Q3A(R2)	1-20
	Hikma and ICH Q3A(R2)	1-20
	Parker and Hikma and ICH Q3A(R2)	1-20
	Parker and ICH Q3B(R2)	1-20
	Hikma and ICH Q3B(R2)	1-20
	Parker and Hikma and ICH Q3B(R2)	1-20
	Parker and Anderson 2000	1-20
	Hikma and Anderson 2000	1-20
	Parker and Hikma and Anderson 2000	1-20
	Parker and Anderson 2012	1-20
	Hikma and Anderson 2012	1-20
	Parker and Hikma and Anderson 2012	1-20
	Parker and Liu	1-20
	Hikma and Liu	1-20
	Parker and Hikma and Liu	1-20
	Parker and Prabu	1-20
	Hikma and Prabu	1-20
	Parker and Hikma and Prabu	1-20
Shah	Parker	1-20
	Silberzweig	1-20
	Bawden	1-20
	Mattner	1-20
	Parker and Silberzweig	1-20
	Parker and Bawden	1-20
	Parker and Mattner	1-20
	Rey	1-20
	Pikal	1-20
	Przic	1-20
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	Parker and Rey	1-20

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Reference	In Combination With	Claims
	Parker and Pikal	1-20
	Parker and Przic	1-20
	Parker and FDA_7/93	1-20
	Bernstein	1-20
	Einfalt	1-20
	Yu	1-20
	Parker and Bernstein	1-20
	Parker and Einfalt	1-20
	Parker and Yu	1-20
	EMEA Guideline	1-20
	ICH Q3A(R2)	1-20
	ICH Q3B(R2)	1-20
	Anderson 2000	1-20
	Anderson 2012	1-20
	Liu	1-20
	Prabu	1-20
	Parker and EMEA Guideline	1-20
	Parker and ICH Q3A(R2)	1-20
	Parker and ICH Q3B(R2)	1-20
	Parker and Anderson 2000	1-20
	Parker and Anderson 2012	1-20
	Parker and Liu	1-20
	Parker and Prabu	1-20

A person having ordinary skill in the art at the time of filing of the ’076 Patent would also have understood the references listed above, alone or in combination, to contain explicit and/or implicit teaching, suggestion, and/or rationales to combine them. It would have been obvious to a person of ordinary skill in the art at the time of the alleged invention to combine a reference with one or more of the other references for the following reasons:

- Combining the prior art limitations according to known methods would have yielded predictable results.
- Simple substitution of one known limitation for another would have yielded predictable results.
- Use of known technique to improve similar pharmaceutical compositions and products in the same way would have been obvious.

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- Applying a known technique to a known pharmaceutical composition and product ready for improvement would have yielded predictable results.
- References disclosing these concepts teach the beneficial utility of them, including as cited in the claim charts submitted herewith.

In addition, a person of ordinary skill in the art would have been motivated to make the combinations based on general industry trends and other considerations discussed in connection with the state of the art. For example, as explained in Section VII.A, which describes the state of the art prior to the alleged dates of alleged inventions in the ’076 Patent, phenobarbital and phenobarbital sodium were widely known and used. Specifically, phenobarbital sodium was known to degrade due to residual water in the composition and/or atmosphere, producing PEAU, 2EPMM, and PBG. Moreover, lyophilization of pharmaceutical compositions and products was well-known and extensively utilized in the industry, particularly for products intended for parenteral administration. As explained in Section VII.B.2.a.i, a POSA would have known that lyophilized phenobarbital sodium drug products were tested as model drugs and were already on the market. Furthermore, as described in Section VII.B.2.a.ii, recognizing lyophilization as a widely employed technique, a POSA would have known that such lyophilized phenobarbital sodium products would be sterile and amorphous. Additionally, a POSA would have known that various dosages of phenobarbital sodium were well-documented and would have been motivated, with a reasonable expectation of success, to produce 65 mg, 100 mg, 130 mg, or 200 mg dosages of lyophilized phenobarbital sodium drug products containing at least 98% phenobarbital sodium in single-use vials. Finally, a POSA would have been motivated, with a reasonable expectation of success, to reduce degradants as much as reasonably practicable.

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A person of ordinary skill in the art at the time of the alleged invention would have combined the references because each generally relates to similar technology. Moreover, to the extent the '076 Patent identifies any needed improvement in the art, the references provide known techniques that would yield the required improvement, and given the finite number of techniques identified, it would have been obvious to try those approaches with a reasonable expectation of success.

The combinations of references provided are exemplary and are not intended to be exhaustive. Additional obviousness combinations of the references identified here are possible, and Sun may rely on such combination(s) in this litigation. In particular, Sun is currently unaware of Plaintiff's allegations with respect to the level of skill in the art and the qualifications of the typical person of ordinary skill in the art. Sun is also unaware of the extent, if any, to which Plaintiff may contend that limitations of the claims at issue are not disclosed in the prior art identified by Sun as anticipatory, and the extent to which Plaintiff will contend that elements not disclosed in the Asserted Patent specifications would have been known to persons of skill in the art. And Sun does not yet know how the Court will construe terms in the claims. Sun is also continuing its investigation of the universe of prior art to identify potential prior art pharmaceutical compositions and products, publications related to those pharmaceutical compositions and products, and third parties that may have information about those pharmaceutical compositions and products. Plaintiff may also be in possession of prior art that Sun may receive as discovery progresses in this case. Sun reserves the right to amend and supplement these contentions to identify other prior art and combinations rendering the claims obvious.

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VIII. SECONDARY CONSIDERATIONS

In view of the minor differences between the claimed subject matter of the Patents-in-Suit and the prior art, any alleged objective evidence of nonobviousness would be insufficient to overcome the strong showing of prima facie obviousness of the claimed inventions.

Plaintiff bears the burden of identifying any secondary considerations relating to the Patents-in-Suit, if any, on which it intends to rely and establishing a nexus between the secondary considerations and the claims. Further, any secondary considerations must be evaluated against the closest prior art. *See, e.g.*, *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999); *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). As such, Sun has no obligation to address secondary considerations of non-obviousness in this submission. Sun reserves the right to respond, amend, or supplement its Invalidity Contentions concerning any evidence or expert reports submitted by Plaintiff concerning such issues.

To be clear, Sun is unaware of any secondary considerations of non-obviousness related to the subject matter claimed in the Patents-in-Suit. Secondary considerations of nonobviousness include commercial success, long felt but unsolved needs, failure of others, copying, unexpected results, industry acclaim, and skepticism of others. To be relevant to nonobviousness, the patentee must establish a nexus between the secondary considerations, such as commercial success, and the claimed invention. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). The patentee must also establish that certain secondary considerations, such as unexpected results, are commensurate in scope with the claims. *See, e.g., Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *In re Harris*, 409 F.3d 1339, 1343-44 (Fed. Cir. 2005). Plaintiff has failed to explain or provide any contentions or evidentiary support for a nexus between any

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asserted claim of the Patents-in-Suit and any secondary consideration. For example, Plaintiff cannot establish a nexus between the subject matter claimed in the Patents-in-Suit and the unsupported statements in the specification and prosecution history, which allege that the lyophilized amorphous phenobarbital sodium formulations produced "surprising, unexpected and desirable results" "in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material." '598 Patent at 2:45-54; '076 Patent at 2:43-62. Nexus is lacking because these statements focus on features that were not novel and they lack a direct relationship to the claimed subject matter in the Patents-in-Suit. Lyophilization was a well-known process for removing water and creating amorphous forms. *See supra* Section VII.A.3. The use of lyophilization to stabilize phenobarbital sodium by reducing moisture and minimizing degradation was expected, not surprising, and lacks a direct relationship to the features of the claimed subject matter and lacks a direct relationship to the features of the claimed subject matter. Since stability-related claims were not novel, any evidence related to this limitation cannot establish nexus. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017); *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356 (Fed. Cir. 2023).

Further to Sun's reservation of rights set forth above, in view of the minor differences between the prior art and the subject matter of the claims of the Patents-in-Suit, any objective evidence of secondary considerations of non-obviousness is insufficient to establish the non-obviousness of the claims. *See, e.g., Novo Nordisk AIS v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013) (claims invalid as obvious despite evidence of "unexpected synergy and commercial success"); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364-65 (Fed. Cir. 2012) ("[t]his case presents a strong case of obviousness based on the prior art references of record," and "even in light of the secondary considerations," the claim at issue

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would have been obvious); *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1368 (Fed. Cir. 2008) ("Secondary considerations of nonobviousness - considered here by the district court - simply cannot overcome this strong prima facie case of obviousness."); *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008) ("In this case, the objective evidence of nonobviousness simply cannot overcome such a strong prima facie case of obviousness."); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) ("The unexpected results and commercial success of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious."); *Bristol-Myers Squibb Co. v. Teva Pharm, USA, Inc.*, 752 F.3d 967, 977-79 (Fed. Cir. 2014) (affirming district court's obviousness holding despite finding there to be some evidence of secondary considerations); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Leapfrog Enters. Inc., v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (despite substantial evidence of commercial success, praise and long-felt need, obviousness conclusion was upheld given the strength of the prima facie obviousness showing).

Fact discovery is still ongoing. Sun reserves the right to amend and update the contentions regarding secondary considerations if and when Plaintiff produces any evidence purporting to support secondary considerations.

IX. THE CLAIMS OF THE PATENTS-IN-SUIT ARE ANTICIPATED BY THE PRIOR ART

Upon information and belief, one or more of the below listed prior art anticipates and/or inherently anticipates the claims of the Patents-in-Suit. Sun reserves the right to prove these references anticipate the claims through fact discovery and expert analysis or testing.

- Nobelbar
- Gardenal
- Sznitowska

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Furthermore, in addition to rendering claims 1-20 of the ’076 Patent obvious, the ’608 Publication renders these claims invalid as anticipated under 35 U.S.C. § 102. Sun incorporates herein all teachings identified above with respect to how the ’608 Publication renders the claims of the ’076 patent obvious. The ’608 Publication discloses a storage stable pharmaceutical product comprising a composition with a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of lyophilized sterile phenobarbital sodium in a single use dose vial. ’608 Publication at Abstract, [0002], [0010], [0025], [0079], [0099]. The ’608 Publication further discloses that the composition comprises no less than 98% phenobarbital sodium. *Id.* at [0010], [0024], [0071], [0103]-[0104], Table 2-3, 7-13, 16. The ’608 Publication also teaches that phenobarbital sodium forms toxic degradation products such as phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) and that once the lyophilized phenobarbital sodium has been reconstituted after storage, the reconstituted solution has “no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG.” *Id.* at [0002], [0006], [0024], [0101]. Specifically, the ’608 Publication teaches reconstituting phenobarbital sodium formulations in 10 mL of Water for Injection or 5% Dextrose and that the lyophilized phenobarbital sodium compositions disclosed in the ’608 Publication “do[] not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.” *Id.* at [0073], [0119]. The ’608 Publication further discloses that “the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at [room temperature] and accelerated

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stability conditions." *Id.* at [0016]; *see also id.* at [0024], [0071], [0090], [0101]. The '608 Publication notes that the accelerated stability conditions are 40° C, 75% RH. *Id.* at [0013], [0016], [0103], Tables 2-3, 10-13, 16. The compositions of the '608 Publication inherently disclose stability for up to 24 months and beyond. Additionally, the '608 Publication discloses "[a] composition of, method for producing, and use of an ***amorphous*** lyophilized Phenobarbital Sodium." *Id.* at Abstract (emphasis added); *see also id.* at [0010]-[0011], [0081]. Thus, the '608 Publication, either expressly or inherently, teaches each and every element of claims 1-20 of the '076 Patent and renders these claims invalid as anticipated.

Finally, in addition to rendering claims 1-20 of the '076 Patent obvious, Shah also renders these claims invalid as anticipated under 35 U.S.C. § 102. Sun incorporates herein all teachings identified above with respect to how Shah renders the claims of the '076 patent obvious. Shah teaches lyophilized phenobarbital sodium compositions present in a concentration of 10-200 mg/mL. Shah at 6:57-64. Furthermore, Shah discloses that the lyophilized phenobarbital sodium incorporates ethanol in concentrations ranging from "about 5000 ppm to about 70000 ppm" to enhance stability and reduce impurity formation. *Id.* at Abstract, 3:3-10, 5:6-11, 6:65-67. Shah also identifies 2-phenyl-2-ethyl acetyl urea (PEAU), 2-phenyl-2-ethyl-malonamide (2EPMM), and α-phenylbutyrylguanidine (PBG) as potential impurities present from the API or generated by the degradation of phenobarbital sodium during the manufacturing or stability of the pharmaceutical compositions. *Id.* at 5:32-40, 6:47-50, cl. 4. Shah also provides that "[o]ne known method of improving the stability of phenobarbital sodium involves the use of a lower pH and the use of a mixture of water and generic solvents such as alcohol, propylene glycol, glycerin, benzyl alcohol, or polyethylene glycol." Shah at 1:43-46. Shah further teaches that "the present disclosure relates to a lyophilized pharmaceutical composition comprising

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phenobarbital sodium and ethanol, wherein ethanol is present in an amount sufficient to inhibit degradation of phenobarbital sodium, such that the amount of total impurities [including PEAU, 2EPMM, and PBG] present following 36 months of storage at 20-25° C. does not exceed 0.2%." Shah at 3:61-67; *see also id.* at 9:62-63, 9:64-10:2. Thus, Shah, either expressly or inherently, teaches each and every element of claims 1-20 of the '076 Patent and renders these claims invalid as anticipated.

X. THE CLAIMS OF THE PATENTS-IN-SUIT ARE INVALID UNDER SECTION 112

A. "a protocol comprising a freezing step, a primary drying step, and a secondary drying step to thereby produce the lyophilized amorphous phenobarbital sodium composition; wherein the freezing step comprises freezing the lyophilized amorphous phenobarbital sodium to a temperature of about −50° C. without application of vacuum; wherein the primary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about −50° C. and about 0° C. for at duration of at least 1,000 minutes; wherein the secondary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about 25° C. and about 50° C. for at duration of at least 200 minutes" (Claims 1-15 of the '598 Patent)

Claim 1 of the '598 Patent recites the element "a protocol comprising a freezing step, a primary drying step, and a secondary drying step to thereby produce the lyophilized amorphous phenobarbital sodium composition," without providing sufficient precision about the parameters of these steps. Although the '598 Patent discloses certain lyophilization parameters such as temperature, pressure, and duration for the freezing, primary drying, and secondary drying steps, *see* '598 Patent at Table 15, this disclosure is inadequate because it does not ensure that a POSA can reasonably ascertain the scope of these elements, particularly "to thereby produce the lyophilized amorphous phenobarbital sodium composition." The lack of specificity surrounding other critical conditions, such as the type of freeze dryer, the configuration of the shelves, the nature of the vacuum system, the loading process of the solution, the precise freezing rate, and

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the method of evacuating the material, renders the claim indefinite and not fully enabled. This omission leaves substantial ambiguity about how these steps are to be performed and how they contribute to producing the lyophilized amorphous phenobarbital sodium composition. Even the additional specificity surrounding the "freezing step" is inadequate as it lacks complete disclosure about the surrounding conditions (e.g., timing). The same is true with the two claimed drying steps as they include a range of pressure, temperature and duration while the disclosure for the lyophilization process is limited to Table 15. Claim 1 recites a primary drying step performed for at least 1000 minutes and a secondary drying step performed for at least 200 minutes, but the specification fails to recite these elements. Nowhere in the specification is 1000 or 200 minutes used. Table 15 shows the primary step was conducted for 1480 and 1220 minutes while the secondary drying step was conducted for 240 and 520 minutes. The same deficiency exists with respect to the claimed pressure ranges, as Table 15 describes pressures of 50 mTorr or 75 mTorr but nothing in between. Further, when 50 mTorr was used, the temperature was increased from -45°C to -42 °C and then held constant. The same lack of disclosure exists with respect to the secondary drying step. There is no written description for a broader temperature range as claimed. No dependent claim provides sufficient specificity to resolve the foregoing issues. Without detailed guidance on these aspects, a POSA would not understand the scope of the invention with reasonable certainty, know if the inventors possessed the full scope of the invention at the time of submitting their application, or be able to practice the full scope of the claims without undue experimentation. This is affirmed by comments within the prosecution history, including by Dr. Dasaradhi Lakakraju. Thus, for this reason, claim 1 (and all claims that depend from it) of the '598 Patent is invalid.

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B. "wherein the freezing step comprises freezing the lyophilized amorphous phenobarbital sodium" (Claims 1-15 of the '598 patent)

Claim 1 indicates that lyophilizing requires a protocol that includes a freezing step, a primary drying step, and a secondary drying step and that protocol produces the lyophilized amorphous product; however, claim 1 also requires that the freezing step involves freezing an already-lyophilized amorphous product. This claim requires a method where the protocol to lyophilize the product and make it amorphous requires three distinct steps while the first step requires that the product to already be lyophilized and amorphous. There is no written description or enablement for this claimed method, and to the extent Plaintiff alleges it requires something different than what it expressly recites, it is confusing. Claim 1 (and all claims that depend from it) is therefore invalid because the ordering of steps makes the claim indefinite, or it lacks written description and enablement.

C. "does not contain an organic solvent" (Claims 1-15 of the '598 patent)

Plaintiff's allegation relating to this claim element renders it invalid for lack of written description, enablement, and/or indefiniteness. The term itself expressly and completely excludes the inclusion of organic solvents. There is no written support for any other conclusion, nor teaching for how to practice the invention with any conclusion. But Plaintiff has somehow still managed to allege that Defendant's product satisfies this claim element. Note again that Plaintiff's infringement contentions are too ambiguous and devoid of substance to understand its position. But Plaintiff's view—whatever it is—lacks written support, enablement, and/or definiteness within the '598 patent.

D. "upon storage" (Claims 1-15 of the '598 patent)

The claim element "upon storage" lacks sufficient specificity concerning how the lyophilized amorphous phenobarbital sodium must be stored, particularly given the stability-

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related elements that must be met. The specification has not provided a full description of "upon storage" to show that the inventors possessed or enabled the full scope of that claim element. Moreover, since various degradation pathways may be affected by different environmental factors, such as temperature and relative humidity, the absence of defined storage conditions renders the term "upon storage" overly broad, and the sheer breadth of the term renders it indefinite. There is no written description or enablement commensurate with the potential scope of this claim element, particularly when the stability-related elements are considered. Claim 1 (and all claims that depend from it) is therefore invalid.

E. "reconstituted in an aqueous solution"/"reconstitution of the lyophilized amorphous phenobarbital sodium in the aqueous solution" (Claims 1-15 of the '598 Patent)

Claims 1, 2, 12, and 13 of the '598 Patent expressly recite the elements "reconstituted in an aqueous solution" or "reconstitution of the lyophilized amorphous phenobarbital sodium in the aqueous solution," without providing sufficient information regarding the parameters of the reconstitution process. All dependent claims similarly include the term(s) and are therefore invalid for the same reasons discussed below. Specifically, there is no disclosure on the testing parameters of the reconstitution, including the timing. Moreover, the '598 Patent allows for the lyophilized phenobarbital sodium to be reconstituted in three different types of aqueous solutions: water for injection, 0.9% saline, or 5% dextrose for intravenous (IV) or intramuscular (IM) administration. '598 Patent at 11:20-23. The '598 Patent fails to disclose how these different solutions might affect the reconstitution process or the degradation of the lyophilized phenobarbital sodium compositions. This lack of specificity regarding reconstitution conditions makes it difficult for a POSA to understand the scope of the claimed invention with reasonable certainty. Thus, for this reason, claims 1-15 of the '598 Patent are invalid as indefinite or for lack of written description or enablement.

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F. "98% lyophilized amorphous phenobarbital sodium" (Claim 15 of the '598 patent)

The patent specification does not clearly show that the inventors possessed or enabled how to make (or measure) the claimed phenobarbital sodium to show that it is at least 98% "lyophilized amorphous." It is further unclear what the 98% is intended to modify. For example, must the claimed composition be 98% lyophilized, amorphous, phenobarbital sodium, or all three? Therefore, this claim element lacks written description, is not enabled, and lacks definiteness.

G. "aqueous solution to form a reconstituted composition," "reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition" (Claims 2-4, 6-15, 17-20 of the '076 Patent)

In the above-identified claims, "reconstituted composition" is used in connection with the concept of measuring the presence and amount of certain impurities; however, there is no disclosure as to when this measurement should take place. Nor is there any description or limitation surrounding what aqueous solution must be used to form the reconstituted composition and still achieve the other claim elements (e.g., relating to stability). For example, must this measurement take place immediately upon reconstitution, must the reconstituted composition forever maintain the impurity levels, or must the reconstituted composition maintain the impurity levels for some alternative time period? Must it achieve any of these with any type of aqueous solution?

Additionally, claims 2-4, 6-11, 13-14, and 18-19 of the '076 Patent further recite the element "reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition," without providing further precision about the parameters of this reconstitution process. Specifically, there is no disclosure on the testing parameters of the reconstitution, including the timing. Moreover, the '076 Patent allows for the lyophilized phenobarbital sodium

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to be reconstituted in three different types of aqueous solutions: water for injection, 0.9% saline, or 5% dextrose for intravenous (IV) or intramuscular (IM) administration. '076 Patent at 11:56-59. The '076 Patent fails to disclose how these different solutions might affect the reconstitution process or the degradation of the lyophilized phenobarbital sodium compositions. Further, the claims themselves are not limited to any particular type of "aqueous solution." This lack of specificity creates significant ambiguity about the solution and reconstitution conditions, making it difficult for a POSA to understand the scope of the claimed invention with reasonable certainty.

Thus, for the reasons set forth above, claims 2-4, 6-15, and 17-20 of the '076 Patent are invalid as indefinite or for lack of written description or enablement.

H. "composition" (Claims 1-20 of the '076 Patent)

Claims 1-20 of the '076 Patent expressly recite the element "composition." The claim language does not restrict the "composition" to a specific physical state. Thus, this claim term is not limited to the amorphous form and can include crystalline form—including 100% crystalline form—of lyophilized phenobarbital sodium.

There is no written description support for this claim term because the disclosure does not reasonably convey to a POSA that the inventors had "possession" of the claimed subject matter, including lyophilized phenobarbital sodium compositions in crystalline form. The specification merely states that "[i]n further experiments, the inventors investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents." '076 Patent at 51:30-33. However, the specification, including Figures 5B and 5C, only shows possession of lyophilized ***amorphous*** phenobarbital sodium. *See id.* at Figs. 5B-5C.

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Further, there is no disclosure of compositions comprising 100 mg or 200 mg of phenobarbital sodium that contain any crystalline amounts. The specification, to the extent it refers at all to crystalline forms of phenobarbital sodium, is limited to 65 mg and 130 mg.

Moreover, there is no enablement to support this claim because the specification does not teach a POSA how to make and use the full scope of the claimed invention, including, for example, a lyophilized phenobarbital sodium composition that is 100% crystalline or even various mixtures thereof. The specification, including Figures 5B and 5C and methods of making storage-stable and highly purified phenobarbital sodium compositions, only shows lyophilized ***amorphous*** phenobarbital sodium compositions. This lack of detailed guidance would require undue experimentation by a POSA to produce a 100% crystalline composition or even mixtures thereof. Further, there is no specific teaching about all the various crystalline forms that may exist or how to make them (e.g., using what solvent in what percentage), the discovery of which would require undue experimentation. Thus, for these reasons, claims 1-4, 6-11, 13-14, and 16-19 of the ’076 Patent are invalid.

Additionally, to the extent the claimed “composition,” may include organic solvents, there is insufficient disclosure to provide written description and enablement for the full scope of the claims. The specification claims that “[t]he presently disclosed formulation does not contain any solvents or preservatives which is specifically advantageous for administration to newborns and neonates.” ’076 Patent at 11:59-62. Subsequently, new matter indicated that the “inventors investigated” “in further experiments” whether stable compositions could be made that included “one or more water miscible co-solvents.” *Id.* at 51:30-33. The potential range of the co-solvent, including organic co-solvents, was claimed to be potentially large, from at 1% to “as high as 90%.” *Id.* at 51:37-52:33. The specification refers only to “isopropanol, tert-butanol, ethanol, and

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acetonitrile as co-solvents." *Id.* at 51:35-36. But the claims are not limited by any type or amount of co-solvent or amount. To the extent Nivagen claims that co-solvents may be included by the claims of the '076 patent, the specification fails to provide adequate written description for or enable the full scope particularly in light of the other comments about organic solvents being deliberately excluded. Further, this inconsistency within the specification renders the claims indefinite.

I. "lyophilized" (Claims 1-20 of the '076 Patent)

The specification of the '076 patent taught only limited protocols for lyophilization, but there are numerous parameters that may be modified. As Nivagen's declarant stated during prosecution of the Patents-in-Suit, "[l]yophilization is a general term for water removal from a composition via sublimation, and numerous process parameters such as temperatures, temperature gradients, degree of vacuum applied, and/or time periods at specific temperatures and partial vacuum can significantly affect the physicochemical properties of the lyophilized product." Declaration of Dr. Dasaradhi Lakakraju Under 37 C.F.R. § 1.132 for Appl. No. 17/025,881 dated May 13, 2021; *see also* Response to Office Action for Appl. No. 18/100,804 dated September 20, 2023 at 6 ("[T]here is a wide range of lyophilization processes and lyophilization conditions (*e.g.*, temperature, pressure, time at the temperature and/or pressure for each of the freezing, primary and secondary drying steps) that will lead to a wide range of physicochemical parameters of the lyophilized product."). Each and every claim of the '076 Patent recites the "general term" "lyophilized" and does not recite any of the "numerous process parameters" identified by Nivagen. The variables at issue for lyophilization, if that term is not obvious, would be too numerous to allow the full scope of any claim of the '076 Patent to have sufficient written description for, nor would they be enabled.

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J. "is stored" (Claims 2-4, 6-15, 17-20 of the '076 Patent)

The claim element "is stored" lacks sufficient specificity concerning how the lyophilized phenobarbital sodium must be stored, particularly given the stability-related elements that must be met. The specification has not provided sufficient disclosure to show that the inventors possessed or enabled the full scope of that claim element. Moreover, since various degradation pathways may be affected by different environmental factors, such as temperature and relative humidity, the lack of defined storage conditions renders the term overly broad, and the sheer breadth of the term renders it at least indefinite, if not also lacking written description and/or enablement.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the above and foregoing document has been served October 22, 2024 to all counsel of record, via E-Mail.

s/ Sam T. Lockner
Samuel T. Lockner

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