Exhibit B-1

Invalidity of U.S. Patent No. 11,878,076 in view of U.S. Publication No. 2021/0085608 A1

U.S. Publication No. 2021/0085608 A1 ("the '608 Publication"), which was published on March 25, 2021, qualifies as prior art under at least 35 U.S.C. §§ 102 and 103 as to the claims 1-20 of U.S. Patent No. 11,878,076 ("the '076 Patent"), as discussed in greater detail in the chart that follows.[1]

To the extent Plaintiff alleges that the '608 Publication does not disclose any particular limitation of claims 1-20 of the '076 Patent, either expressly or inherently, it would have been obvious to a person of ordinary skill in the art as of the priority date of the '076 Patent to modify and/or to combine the teachings of the '608 Publication, including but not limited to the prior art references presently found in Sun's Invalidity Contentions and any supplements thereto and the relevant section of charts for other prior art for the '076 Patent in a manner that would have rendered the claims 1-20 invalid as obvious. The inclusion of the particular limitation into the pharmaceutical compositions and products described in the '608 Publication would have been obvious for at least the following reasons: It would have been obvious to modify the pharmaceutical compositions and products described in the '608 Publication, alone or in combination with the references identified in Section VII.B.2 of Sun's Invalidity Contentions, to meet this limitation based on: (a) the teachings in the '608 Publication itself; (b) a person of ordinary skill in the art implementing a predictable variation of the pharmaceutical compositions and products described in the '608 Publication or in the other identified references; (c) the logic, judgment, intelligence, creativity, innovation and common sense a person of ordinary skill in the art would employ; (d) the inferences

[1] Nothing in these claim charts should be construed as an admission regarding infringement, either literally or under the doctrine of equivalents, or as an admission regarding Sun's understanding of the proper scope of the claims of the '076 Patent. Given Plaintiff's vague and ambiguous infringement contentions, the exemplary citations herein necessarily account for a variety of possible infringement arguments and claim constructions. Sun reserves the right to rely on additional citations or sources of evidence that also may be applicable, or that may become applicable in light of claim construction, changes in Plaintiff's infringement contentions, and/or information obtained during discovery as the case progresses, including, but not limited to, third-party discovery related to any pharmaceutical product available at the time of the alleged invention. Various positions put forth in this document are predicated on Plaintiff's overly broad interpretation of its claims as evidenced by the infringement allegations received to date. Those positions are not intended to and do not necessarily reflect Sun's interpretation of the true and proper scope of Plaintiff's claims, and Sun reserves the right to adopt claim construction positions that differ from or even conflict with various positions put forth in this document.

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and creative and routine steps that a person of ordinary skill in the art would employ; (e) market demand for pharmaceutical compositions and products to include this limitation; and/or (f) design needs or market pressures to solve a problem with a finite number of solutions that could have produced the desired outcome.

Sun reserves the right to amend or supplement this claim chart pursuant to the Docket Control Order issued by the Court on September 27, 2024 (Dkt. No. 37).

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A. Claim 1

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[1p] A storage stable pharmaceutical product, comprising:	To the extent the preamble is limiting, the '608 Publication discloses and/or renders obvious the preamble based on at least the following citations. *See, e.g.*: • '608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • '608 Publication at [0002] The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water. • '608 Publication at [0009] Accordingly, there is still a need for a stable Phenobarbital Sodium formulation in a formulation that is storage stable and void or essentially void of degradation impurities upon solubilization in water. • '608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • '608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising

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	and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0015] For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl). • ’608 Publication at [0016] 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

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	(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. • ’608 Publication at [0018] Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization. • ’608 Publication at [0019] Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum. • ’608 Publication at [0026] Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073]

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	In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0074] The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (e.g., Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of the Phenobarbital Sodium is preferably USP “purified” or “practical” (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to FIG. 5A, an X-ray powder diffraction (XRPD) pattern is shown of this compound. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0082]

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	Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The

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	lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 2 2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9

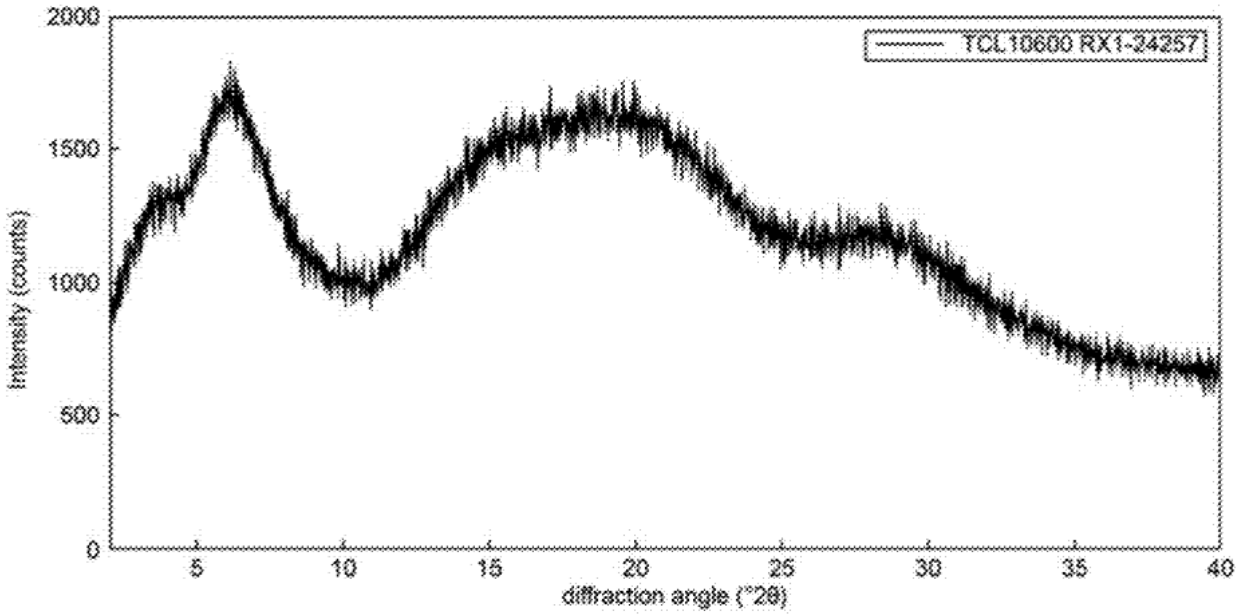
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	9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 10 10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose the preamble, a person of ordinary skill in the art would have determined that the preamble is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of the preamble given, at the very least, the person’s understanding of the state of the art, the problems

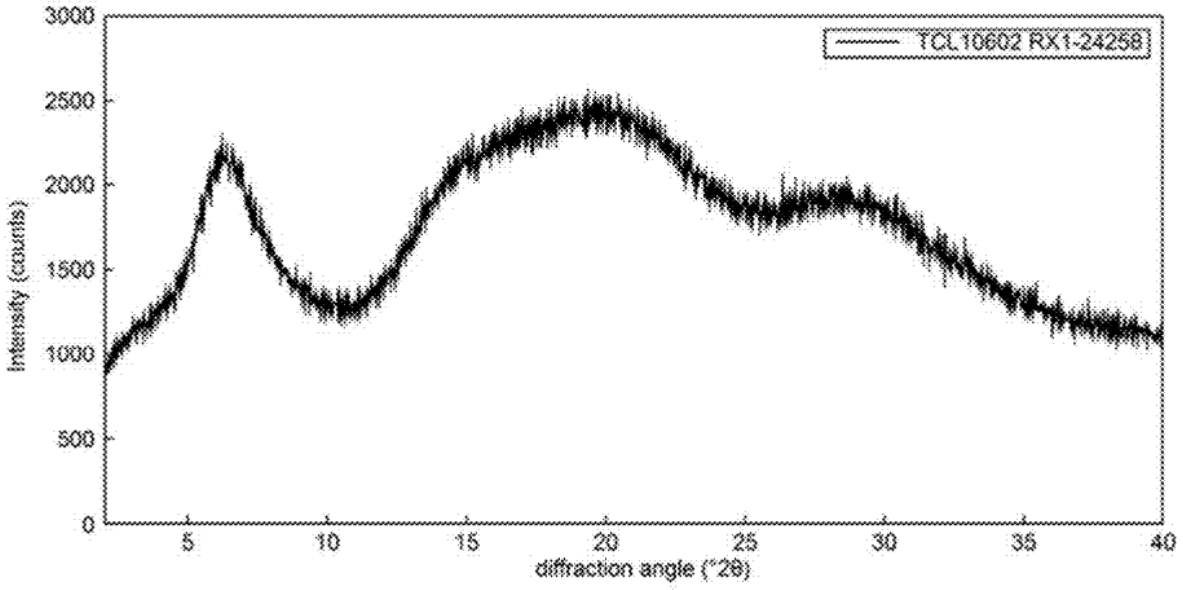
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	addressed and solved in the prior art, and the teachings of the ’608 Publication.
[1a] a single use dose vial, and	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems

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	addressed and solved in the prior art, and the teachings of the ’608 Publication.
[1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0008] In addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (e.g., Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL), includes organic solvents such as alcohol, which are not desirable in general and indeed not suitable for administration to newborns as described in the art, e.g., Williams et al., 1998, “Evaluating Toxic Alcohol Poisoning in the Emergency Setting,” Laboratory Medicine, Vol. 29, No. 2; Wood et al., 2007, *J. of Perinatology*, 27:183-185; Kumar, 1985, “Adverse Drug Reactions in the Newborn,” *Annals of Clin. And Lab. Sci*, Vol. 15, No. 3; and Cuzzolin, 2018, J. *Pediatric and Neonatal Individualized Med.*, doi:10.7363/070112. • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

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	Fig. 5C  • ’608 Publication at [0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30

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	minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. • ’608 Publication at [0093] In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

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	• ’608 Publication at [0102], Table 1 In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in Table 1. Representative chromatograms from HPLC analysis are shown in FIGS. 2A-2H, 3A-3L, and 4A-4L.

TABLE 1

Formulation Details

Dosage form		Liquid	Lyophilized
Components	Chemical name	mg/mL	mg/vial
Drug Substance	Phenobarbital Sodium	65 or 130	65 or 130
Inactive ingredients	Propylene Glycol	705	NA
	Benzyl alcohol	15.6	NA
	Ethanol	78.9	NA
	HCL	For pH adjustment	NA
	Water for Injection	QS (Quantity Supplied)	NA

Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial
Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL

	• ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for

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	Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

’076 Patent Claim Limitation	The ’608 Publication
	• ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 9).

’076 Patent Claim Limitation	The ’608 Publication

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

’076 Patent Claim Limitation	The ’608 Publication

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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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 Claim Limitation	The ’608 Publication

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

’076 Patent Claim Limitation	The ’608 Publication
	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

’076 Patent Claim Limitation	The ’608 Publication

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

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

’076 Patent Claim Limitation	The ’608 Publication

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

’076 Patent Claim Limitation	The ’608 Publication

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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0122], Table 14

Data for Osmolality , Particulate matter and assay for Sodium Chloride is disclosed in Table 14

TABLE 14

Phenobarbital Sodium for Injection, USP, 200 mg/vial in Water or Sodium Chloride - Osmolality, Particulate Matter and Assay for Sodium Chloride.

Batch No	Osmolality* (mOsmol/Kg) (Specification: To be reported) Reconstitution in 10 mL (20 mg/mL)	Particulate Matter (By Light Obscuration method) Ref: USP<788> ≥10 µM Specification: (NMT 6000 particles/vial)	Particulate Matter (By Light Obscuration method) Ref: USP<788> ≥25 µM Specification: (NMT 600 particles/vial	Assay of Sodium Chloride (titrimetric; Ref USP monograph for Sodium Chloride Injection Specification: (95.0%-105.0%)
NPH2031A (200 mg/vial)	148	80.0	0.67	NA
NPH2031B (200 mg/vial) (Phenobarbital Sodium 200 mg, 9% Sodium Chloride)	372	171	1.33	99.99
Water-Blank	0	NA	NA	NA
0.9% Sodium Chloride	270	NA	NA	NA

- ’608 Publication at [0123], Table 15

’076 Patent Claim Limitation	The ’608 Publication
	Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in Table 15.

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)

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at Table 17

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TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

- ’608 Publication at claim 13

13. The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

- ’608 Publication at claim 19

19. The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

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	To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[1c] wherein the composition is sterile and lyophilized, and	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Title Lyophilized Compositions of Phenobarbital Sodium Salt • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0002] The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium.

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	• ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0015] For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl). • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0018] Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization. • ’608 Publication at [0019] Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum. • ’608 Publication at [0020] Aspects of the present disclosure also include a method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, in which the method includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, adjusting the pH of the

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	Phenobarbital Sodium solution to or between 9.2 to 10.2, and lyophilizing the Phenobarbital Sodium solution to form stable white lyophilized powder of Phenobarbital Sodium. • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0026] Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization. • ’608 Publication at [0027]

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	Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0074] The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (e.g., Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of

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	the Phenobarbital Sodium is preferably USP “purified” or “practical” (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to FIG. 5A, an X-ray powder diffraction (XRPD) pattern is shown of this compound. • ’608 Publication at [0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg

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	doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. • ’608 Publication at [0080] In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089]

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	In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0094] In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing. • ’608 Publication at [0095] In another embodiment, the method further includes aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum.

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	• ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0102], Table 1 In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in Table 1. Representative chromatograms from HPLC analysis are shown in FIGS. 2A-2H, 3A-3L, and 4A-4L.

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TABLE 1

Formulation Details

Dosage form		Liquid	Lyophilized
Components	Chemical name	mg/mL	mg/vial
Drug Substance	Phenobarbital Sodium	65 or 130	65 or 130
Inactive ingredients	Propylene Glycol	705	NA
	Benzyl alcohol	15.6	NA
	Ethanol	78.9	NA
	HCL	For pH adjustment	NA
	Water for Injection	QS (Quantity Supplied)	NA

Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial
Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL

- ’608 Publication at [0103], Tables 2-3

With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and

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	130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

’076 Patent Claim Limitation	The ’608 Publication
	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0108] Lyophilization parameters for the lyophilization microscopy including a start temperature of −50° C. with heating at 1° C./minute to −40° C. followed by heating at 0.5° C./minute to −32.0° C. • ’608 Publication at [0120], Tables 7-9

’076 Patent Claim Limitation	The ’608 Publication
	These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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
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

’076 Patent Claim Limitation	The ’608 Publication

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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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 Claim Limitation	The ’608 Publication

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

’076 Patent Claim Limitation	The ’608 Publication
	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

’076 Patent Claim Limitation	The ’608 Publication

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

’076 Patent Claim Limitation	The ’608 Publication

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

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

’076 Patent Claim Limitation	The ’608 Publication

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

’076 Patent Claim Limitation	The ’608 Publication

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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0123], Table 15

Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in Table 15.

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)

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

’076 Patent Claim Limitation	The ’608 Publication
	• ’608 Publication at Table 17 TABLE 17 Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details. | Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL) | |---|---|---|---|---|
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA	 Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose Proposed Reconstitution Volume: 5 mL • ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 2 2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method

’076 Patent Claim Limitation	The ’608 Publication
	comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 10 10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

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	• ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at claim 14 14. The method of claim 2, further comprising filtering the Phenobarbital Sodium solution prior to lyophilizing. • ’608 Publication at claim 15 15. The method of claim 2, further comprising: aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant

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	section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[1d] wherein the composition comprises no less than 98% phenobarbital sodium.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide

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	(2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0120], Tables 7-9 These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill

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	in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

B. Claim 2

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[2p] The pharmaceutical product of claim 1,	*See supra* Claim 1.
[2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics.

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	However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016]

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	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. • '608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • '608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • '608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than

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	97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082]

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	Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101]

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	Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations

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	at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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) 2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 2

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a

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	reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

C. Claim 3

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[3p] The pharmaceutical product of claim 1,	*See supra* Claim 1.
[3a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with

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more than 0.05% PEAU.	an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium

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	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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

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	• ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of

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	action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized

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	Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of

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	PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a

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	reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

D. Claim 4

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[4p] The pharmaceutical product of claim 1,	*See supra* Claim 1.
[4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with

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2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).	an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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).

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	• ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic

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	degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101]

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	Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations

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	at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 9).

’076 Patent Claim Limitation	The ’608 Publication

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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

’076 Patent Claim Limitation	The ’608 Publication
	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

’076 Patent Claim Limitation	The ’608 Publication

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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 10

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

E. Claim 5

’076 Patent Claim Limitation	The ’608 Publication
[5p] The pharmaceutical	*See supra* Claim 1.

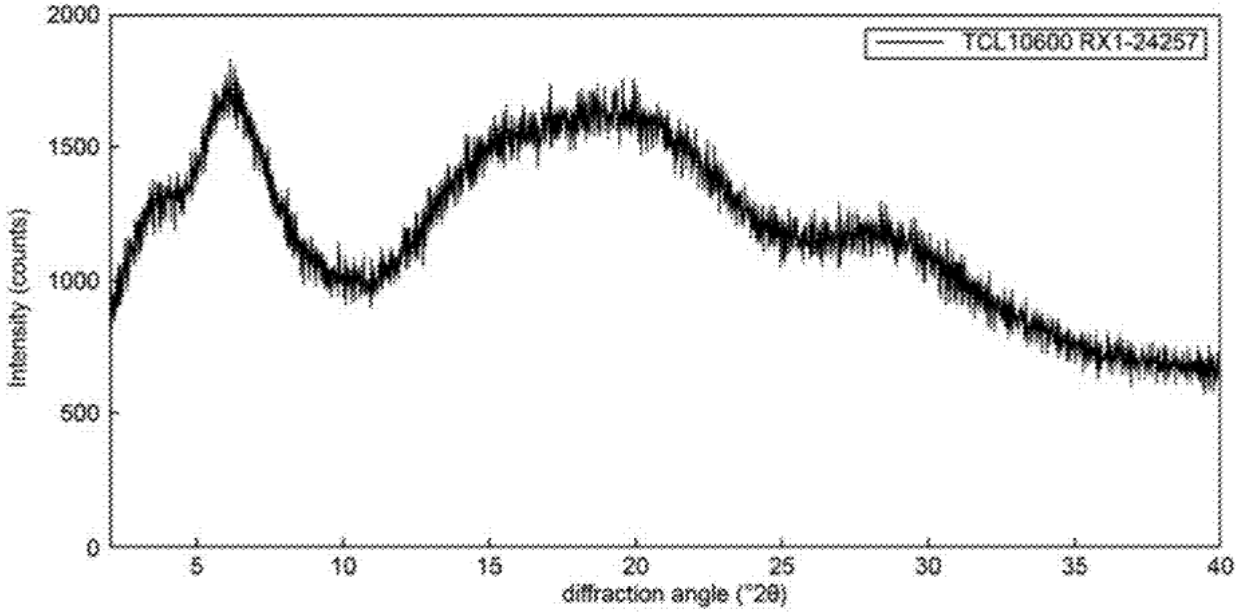
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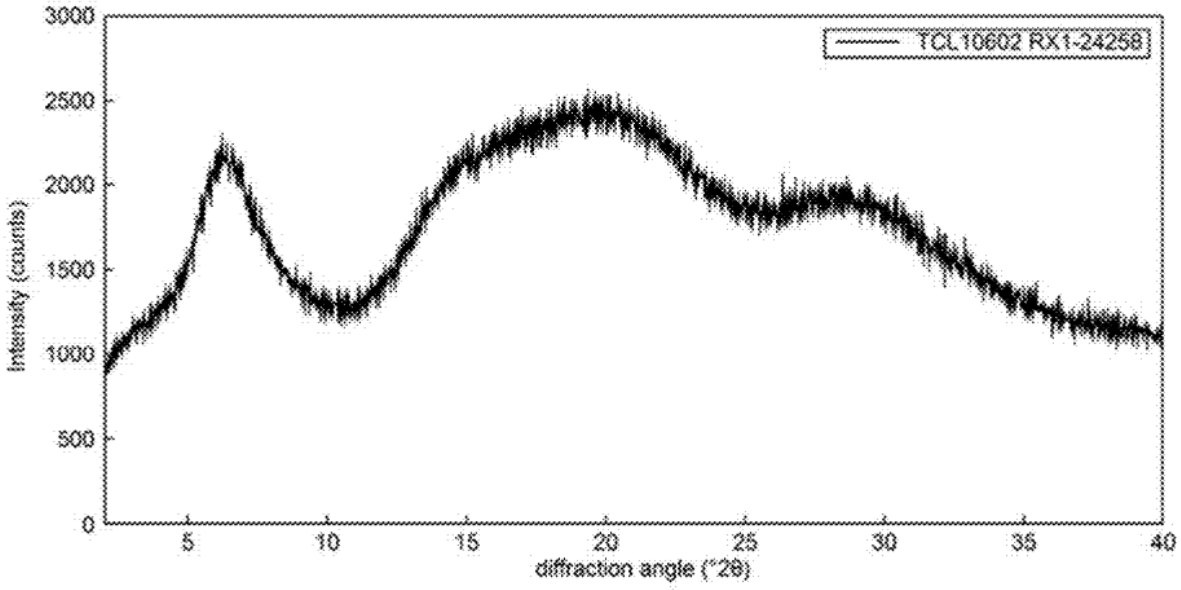
’076 Patent Claim Limitation	The ’608 Publication
product of claim 1,	
[5a] wherein the composition is amorphous.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0012] Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%,

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	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.). • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

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	Fig. 5C  • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to

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	embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

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	• ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

F. Claim 6

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[6p] The pharmaceutical product of claim 1,	*See supra* Claim 1.
[6a] wherein the composition has the property that when the composition is stored at room temperature for 24	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium

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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).	having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage.

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	• ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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).

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	• ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic

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	degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

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	• ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and

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	the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a

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	reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

G. Claim 7

’076 Patent Claim Limitation	The ’608 Publication
[7p] A pharmaceutical product, comprising:	To the extent the preamble is limiting, the ’608 Publication discloses and/or renders obvious the preamble based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0002] The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water. • ’608 Publication at [0009]

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	Accordingly, there is still a need for a stable Phenobarbital Sodium formulation in a formulation that is storage stable and void or essentially void of degradation impurities upon solubilization in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection.

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	• ’608 Publication at [0015] For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl). • ’608 Publication at [0016] 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. • ’608 Publication at [0018] Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization. • ’608 Publication at [0019] Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum. • ’608 Publication at [0026] Additional aspects of the present disclosure include a pharmaceutical product including a vial

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	containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0074] The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified

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	Phenobarbital Sodium solid is purchased from a chemical supplier (e.g., Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of the Phenobarbital Sodium is preferably USP “purified” or “practical” (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to FIG. 5A, an X-ray powder diffraction (XRPD) pattern is shown of this compound. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the

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	lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 2 2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method

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	comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 10 10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

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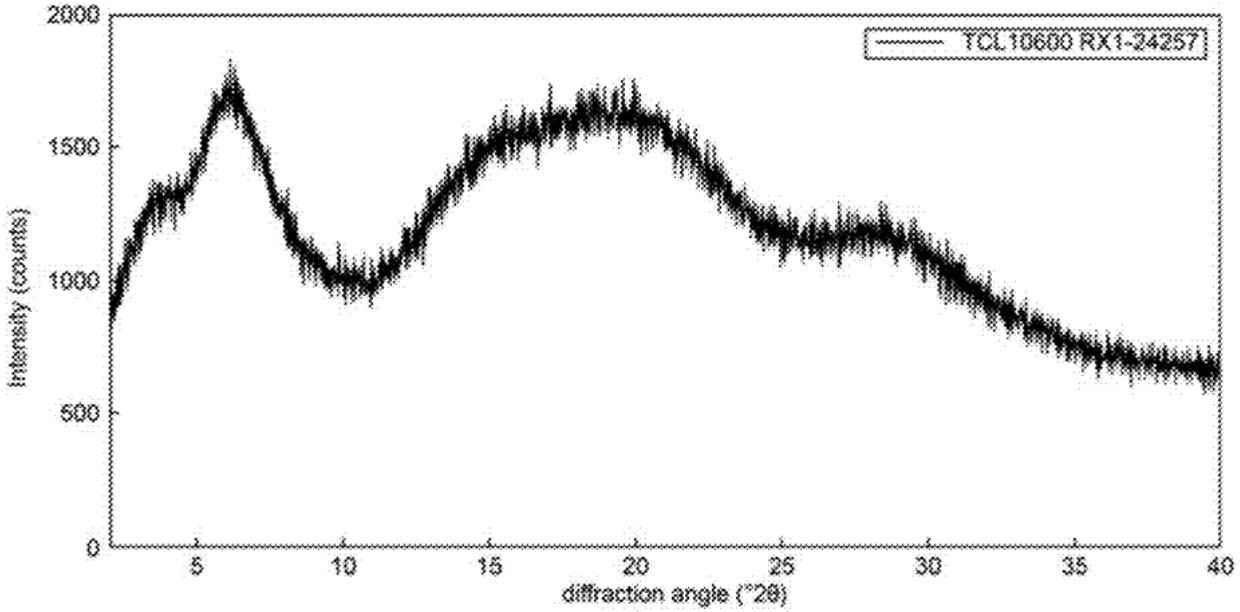
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	• ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose the preamble, a person of ordinary skill in the art would have determined that the preamble is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of the preamble given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[7a] a single use dose vial, and	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a

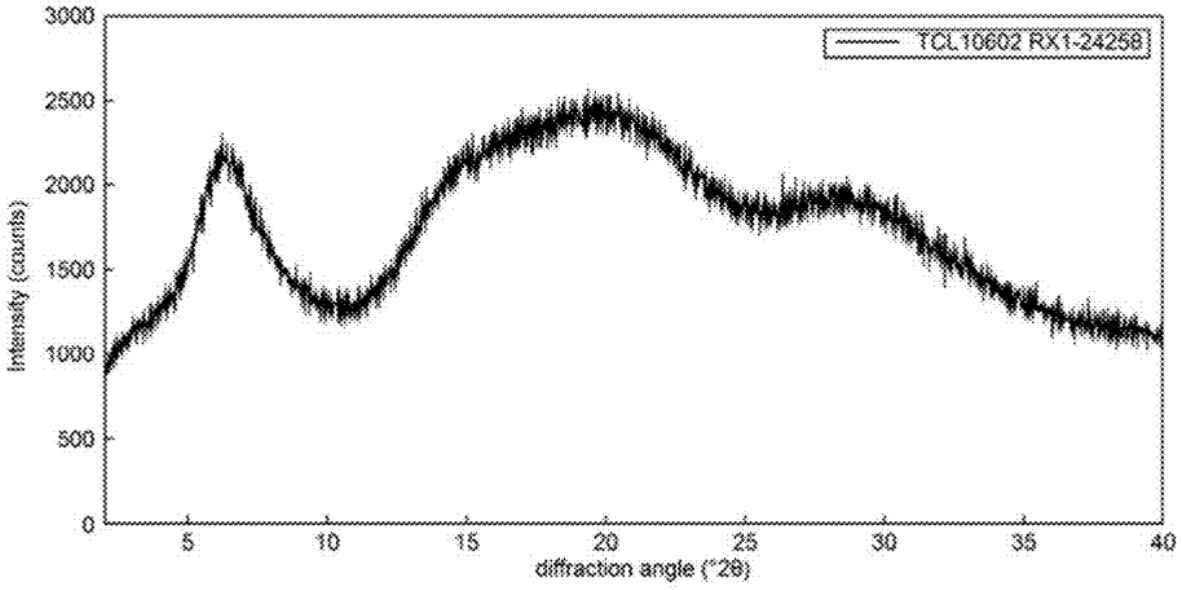
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	specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[7b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0008] In addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (e.g., Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL), includes organic solvents such as alcohol, which are not desirable in general and indeed not suitable for administration to newborns as described in the art, e.g., Williams et al., 1998, “Evaluating Toxic Alcohol Poisoning in the Emergency Setting,” Laboratory Medicine, Vol. 29, No. 2; Wood et al., 2007, *J. of Perinatology*, 27:183-185; Kumar, 1985, “Adverse Drug Reactions in the Newborn,” *Annals of Clin. And Lab. Sci*, Vol. 15, No. 3; and Cuzzolin, 2018, J. *Pediatric and Neonatal Individualized Med.*, doi:10.7363/070112. • ’608 Publication at [0025]

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	Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

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	Fig. 5C  • ’608 Publication at [0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30

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	minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. • ’608 Publication at [0093] In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

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	• ’608 Publication at [0102], Table 1 In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in Table 1. Representative chromatograms from HPLC analysis are shown in FIGS. 2A-2H, 3A-3L, and 4A-4L. TABLE 1 Formulation Details Dosage form: Liquid / Lyophilized Components | Chemical name | mg/mL | mg/vial Drug Substance | Phenobarbital Sodium | 65 or 130 | 65 or 130 Inactive ingredients | Propylene Glycol | 705 | NA Benzyl alcohol | 15.6 | NA Ethanol | 78.9 | NA HCL | For pH adjustment | NA Water for Injection | QS (Quantity Supplied) | NA Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for

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	Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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 Claim Limitation	The ’608 Publication

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0122], Table 14

Data for Osmolality , Particulate matter and assay for Sodium Chloride is disclosed in Table 14

TABLE 14

Phenobarbital Sodium for Injection, USP, 200 mg/vial in Water or Sodium Chloride - Osmolality, Particulate Matter and Assay for Sodium Chloride.

Batch No	Osmolality* (mOsmol/Kg) (Specification: To be reported) Reconstitution in 10 mL (20 mg/mL)	Particulate Matter (By Light Obscuration method) Ref: USP<788> ≥10 µM Specification: (NMT 6000 particles/vial)	Particulate Matter (By Light Obscuration method) Ref: USP<788> ≥25 µM Specification: (NMT 600 particles/vial	Assay of Sodium Chloride (titrimetric; Ref USP monograph for Sodium Chloride Injection Specification: (95.0%-105.0%)
NPH2031A (200 mg/vial)	148	80.0	0.67	NA
NPH2031B (200 mg/vial) (Phenobarbital Sodium 200 mg, 9% Sodium Chloride)	372	171	1.33	99.99
Water-Blank	0	NA	NA	NA
0.9% Sodium Chloride	270	NA	NA	NA

- ’608 Publication at [0123], Table 15

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	Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in Table 15.

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)

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at Table 17

’076 Patent Claim Limitation	The ’608 Publication

TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

- ’608 Publication at claim 13

13. The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

- ’608 Publication at claim 19

19. The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

’076 Patent Claim Limitation	The ’608 Publication
	To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[7c] wherein the composition is sterile and lyophilized,	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Title Lyophilized Compositions of Phenobarbital Sodium Salt • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0002] The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium.

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	• ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0015] For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl). • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0018] Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization. • ’608 Publication at [0019] Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum. • ’608 Publication at [0020] Aspects of the present disclosure also include a method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, in which the method includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, adjusting the pH of the

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	Phenobarbital Sodium solution to or between 9.2 to 10.2, and lyophilizing the Phenobarbital Sodium solution to form stable white lyophilized powder of Phenobarbital Sodium. • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0026] Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization. • ’608 Publication at [0027]

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	Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0074] The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (e.g., Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of

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	the Phenobarbital Sodium is preferably USP “purified” or “practical” (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to FIG. 5A, an X-ray powder diffraction (XRPD) pattern is shown of this compound. • ’608 Publication at [0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending 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). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to 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. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg

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	doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium. • ’608 Publication at [0080] In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089]

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	In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0094] In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing. • ’608 Publication at [0095] In another embodiment, the method further includes aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum.

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	• ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0102], Table 1 In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in Table 1. Representative chromatograms from HPLC analysis are shown in FIGS. 2A-2H, 3A-3L, and 4A-4L.

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TABLE 1

Formulation Details

Dosage form		Liquid	Lyophilized
Components	Chemical name	mg/mL	mg/vial
Drug Substance	Phenobarbital Sodium	65 or 130	65 or 130
Inactive ingredients	Propylene Glycol	705	NA
	Benzyl alcohol	15.6	NA
	Ethanol	78.9	NA
	HCL	For pH adjustment	NA
	Water for Injection	QS (Quantity Supplied)	NA

Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial
Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL

- ’608 Publication at [0103], Tables 2-3

With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and

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	130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0108] Lyophilization parameters for the lyophilization microscopy including a start temperature of −50° C. with heating at 1° C./minute to −40° C. followed by heating at 0.5° C./minute to −32.0° C. • ’608 Publication at [0120], Tables 7-9

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	These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0123], Table 15

Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in Table 15.

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)

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	• ’608 Publication at Table 17

TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

- ’608 Publication at claim 1

1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium.

- ’608 Publication at claim 2

2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method

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	comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 10 10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

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	• ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at claim 14 14. The method of claim 2, further comprising filtering the Phenobarbital Sodium solution prior to lyophilizing. • ’608 Publication at claim 15 15. The method of claim 2, further comprising: aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant

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	section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[7d] wherein the composition comprises no less than 98% phenobarbital sodium, and	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide

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	(2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0120], Tables 7-9 These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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) 2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill

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	in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.
[7e] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% phenylethylacetylurea (PEAU).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007]

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	Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071]

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	The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088]

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	In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently

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	disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 2

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a

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	reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

H. Claim 8

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[8p] The pharmaceutical product of claim 7,	*See supra* Claim 7.
[8a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with

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more than 0.05% PEAU.	an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium

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	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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

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	• ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of

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	action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized

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	Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of

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	PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a

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	reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

I. Claim 9

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[9p] The pharmaceutical product of claim 7,	*See supra* Claim 7.
[9a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with

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more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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).

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	• ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic

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	degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101]

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	Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations

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	at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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)	NMT 0.2%	BQL	ND	ND
2EPMM				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

J. Claim 10

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[10p] The pharmaceutical	*See supra* Claim 7.

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product of claim 7,	
[10a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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.

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	• ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

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’076 Patent Claim Limitation	The ’608 Publication
	• ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and

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	the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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				
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

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

K. Claim 11

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[11p] The pharmaceutical	*See supra* Claim 10.

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product of claim 10,	
[11a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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.

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	• ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

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	• ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and

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	the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

L. Claim 12

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[12p] The pharmaceutical	*See supra* Claim 7.

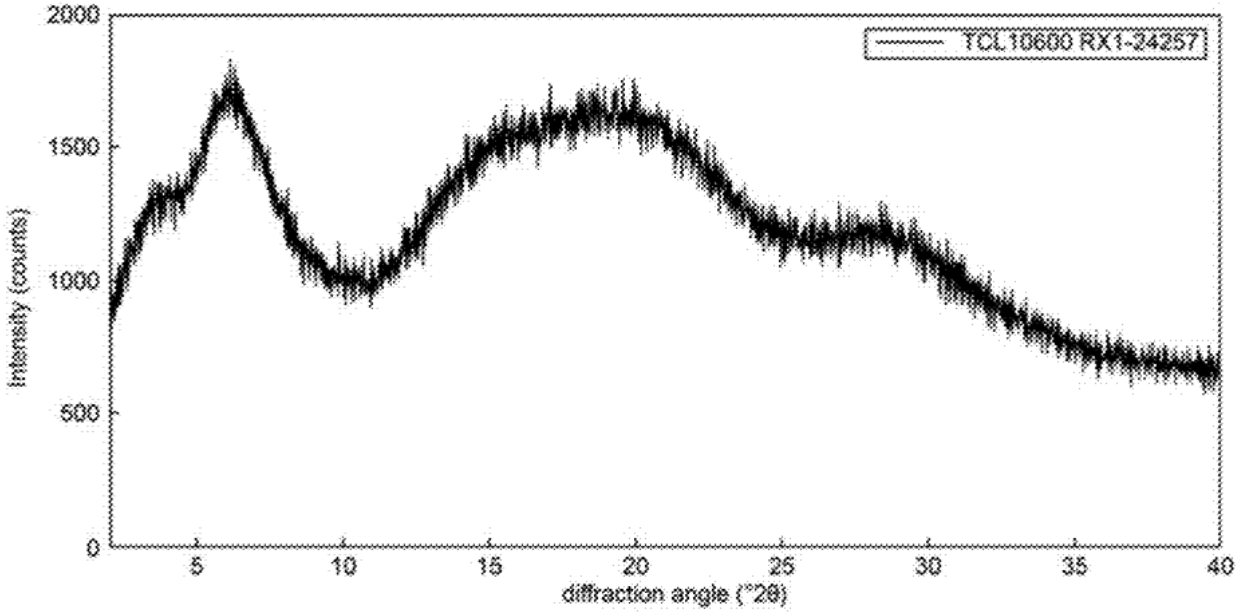
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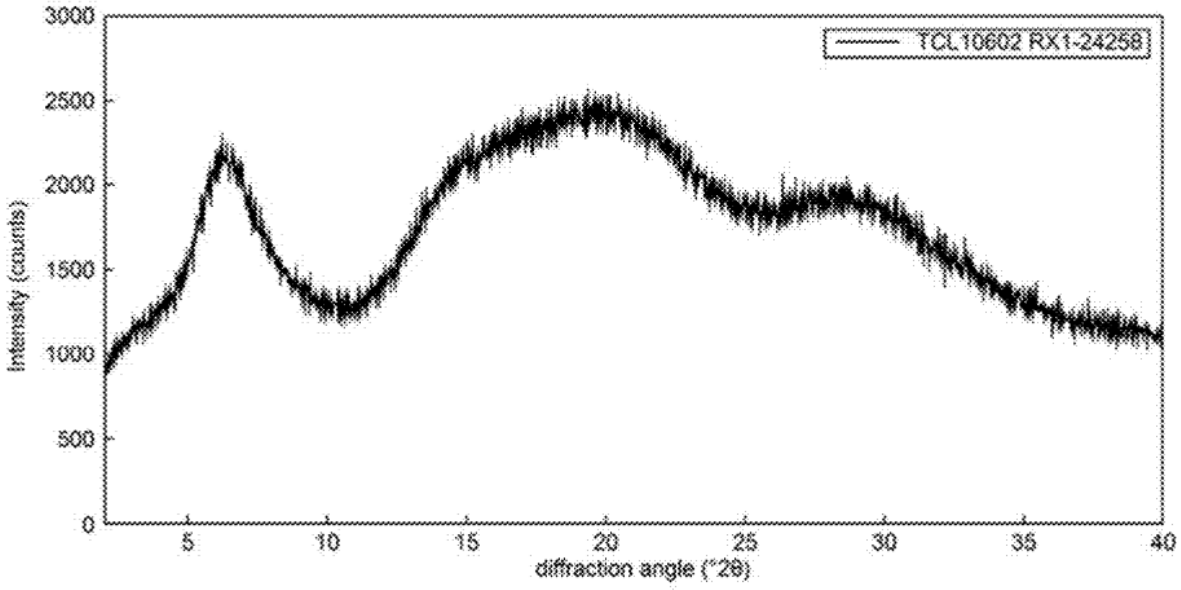
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product of claim 7,	
[12a] wherein the composition is amorphous.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0012] Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%,

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	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.). • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

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	Fig. 5C  • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to

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	embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

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	• ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

M. Claim 13

’076 Patent Claim Limitation	The ’608 Publication
[13p] The pharmaceutical product of claim 12,	*See supra* Claim 12.
[13a] wherein the composition has the property that when the composition is stored at room temperature for 6	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium

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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).	having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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. • ’608 Publication at [0017]

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	According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions

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	which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding

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	the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and

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	130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 10

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

N. Claim 14

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[14p] The pharmaceutical	*See supra* Claim 1.

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product of claim 1,	
[14a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% PEAU, and wherein the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the

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	hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage. • ’608 Publication at [0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium 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. In some embodiments, the water is Water for Injection. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital

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	Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water,

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	the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at [0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

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	• ’608 Publication at [0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection,

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	0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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				
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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 2

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	2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution. • ’608 Publication at claim 8 8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 9 9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 10 10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6

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’076 Patent Claim Limitation	The ’608 Publication
	months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

O. Claim 15

’076 Patent Claim Limitation	The ’608 Publication
[15p] The pharmaceutical product of claim 14,	*See supra* Claim 14.
[15a] wherein the composition is amorphous.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable

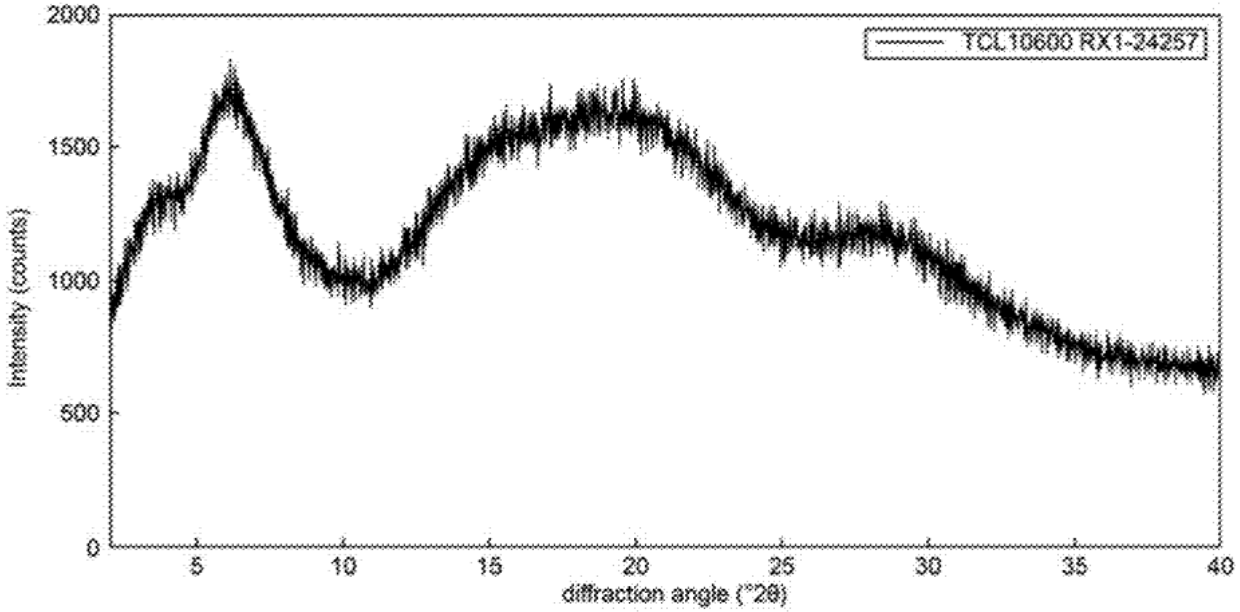
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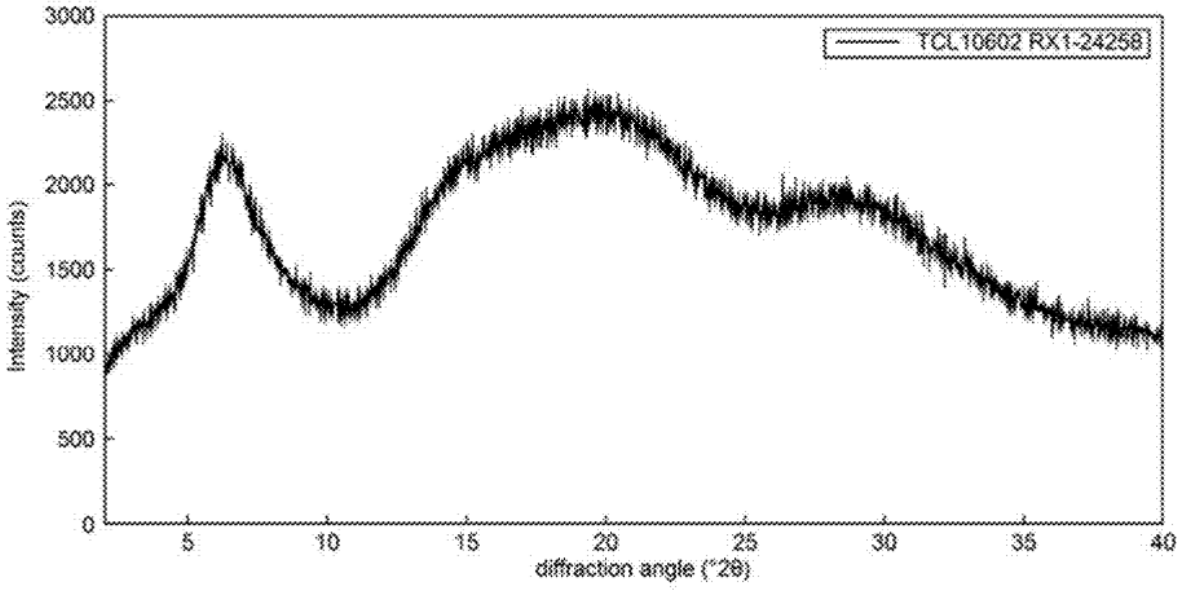
’076 Patent Claim Limitation	The ’608 Publication
	being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0012] 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.). • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is

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	equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

’076 Patent Claim Limitation	The ’608 Publication
	Fig. 5C  • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to

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	embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

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’076 Patent Claim Limitation	The ’608 Publication
	• ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

P. Claim 16

’076 Patent Claim Limitation	The ’608 Publication
[16p] The pharmaceutical product of claim 1,	*See supra* Claim 1.
[16a] wherein the product comprises the 100 mg dose in the single use dose vial.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of

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	Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0093] In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg. • ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital

’076 Patent Claim Limitation	The ’608 Publication
	Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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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	90.0%-105.0%	98.4	97.8	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6
Phenobarbital Sodium Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	ND	ND	ND	ND
2EPMM															
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

TABLE 16-continued

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

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

- ’608 Publication at Table 17

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TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

- ’608 Publication at claim 13

13. The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

- ’608 Publication at claim 19

19. The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

’076 Patent Claim Limitation	The ’608 Publication
	To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

Q. Claim 17

’076 Patent Claim Limitation	The ’608 Publication
[17p] The pharmaceutical product of claim 7,	*See supra* Claim 7.
[17a] wherein the product comprises the 100 mg dose in the single use dose vial.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0075]

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’076 Patent Claim Limitation	The ’608 Publication
	Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C. • ’608 Publication at [0093] In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg. • ’608 Publication at [0105] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL. • ’608 Publication at [0106] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65

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’076 Patent Claim Limitation	The ’608 Publication
	mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride. TABLE 6 Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details. NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL Ingredients | Manufacturer | mg/mL (after reconstitution) | mg/vial | mg/mL (after reconstitution) | mg/vial Phenobarbital Sodium | Siegfried USA, LLC | 20 | 200 | 20 | 200 • ’608 Publication at [0124], Table 16

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’076 Patent Claim Limitation	The ’608 Publication
	Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at Table 17

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TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

- ’608 Publication at claim 13

13. The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

- ’608 Publication at claim 19

19. The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

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	To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

R. Claim 18

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[18p] The pharmaceutical product of claim 8,	*See supra* Claim 8.
[18a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects.

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	Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes

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	reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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. • ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or

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	hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The

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	lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit

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	(BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

S. Claim 19

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[19p] The pharmaceutical	*See supra* Claim 8.

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product of claim 8,	
[19a] wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, 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). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate. • ’608 Publication at [0016] 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

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	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. • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution. • ’608 Publication at [0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, 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.

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	• ’608 Publication at [0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU). • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

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	• ’608 Publication at [0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at [0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT. • ’608 Publication at [0103], Tables 2-3 With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. 3A-3F, FIGS. 4A-4F), and

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	the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. 3G-3L, FIGS. 4G-4L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

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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) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
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											
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

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	• ’608 Publication at [0104] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG. • ’608 Publication at [0119], Table 6 Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

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TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200

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TABLE 6-continued

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear		Wheaton Part#223686			
20 mm Igloo Bromobutyl stopper		Datwyler			
Seal 20 mm Filp-Cap, Red		Wheaton Part# 224203			

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

- ’608 Publication at [0120], Tables 7-9

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 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

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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

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
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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)

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								
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)

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

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

- ’608 Publication at [0121], Tables 10-13

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	Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

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

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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

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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

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)				
2EPMM	NMT 0.2%	ND	ND	ND
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

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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) 2EPMM	NMT 0.2%	BQL	ND	ND

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

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’076 Patent Claim Limitation	The ’608 Publication

- ’608 Publication at [0124], Table 16

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

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;

- ’608 Publication at claim 10

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	10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC). • ’608 Publication at claim 11 11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT). • ’608 Publication at claim 12 12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

T. Claim 20

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[20p] The pharmaceutical	*See supra* Claim 8.

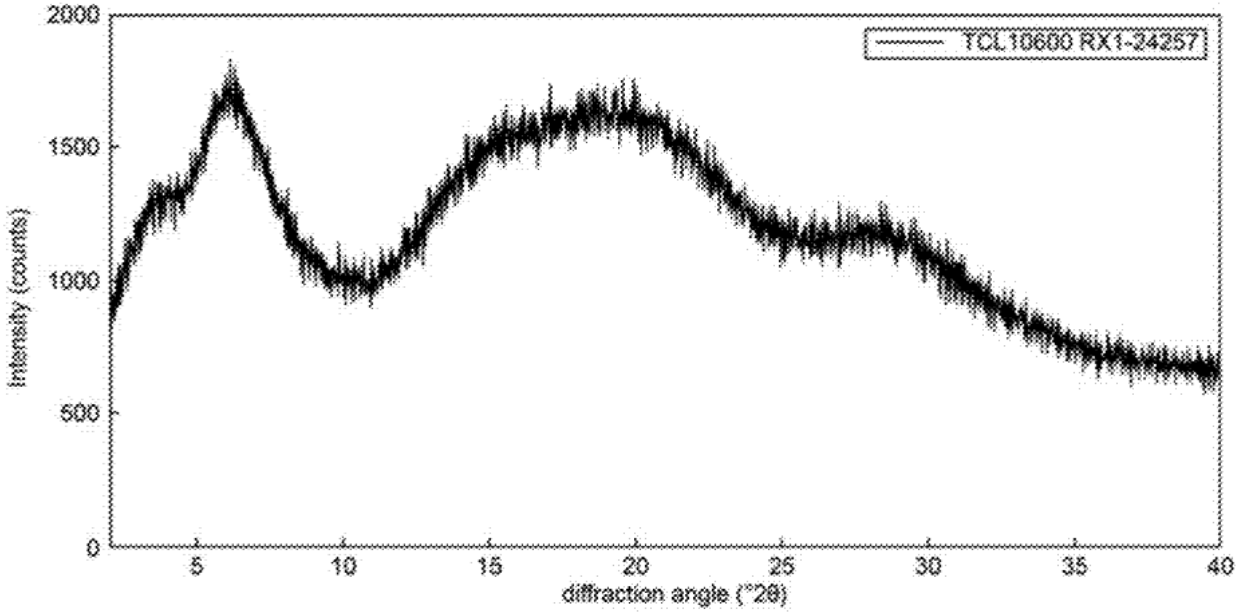
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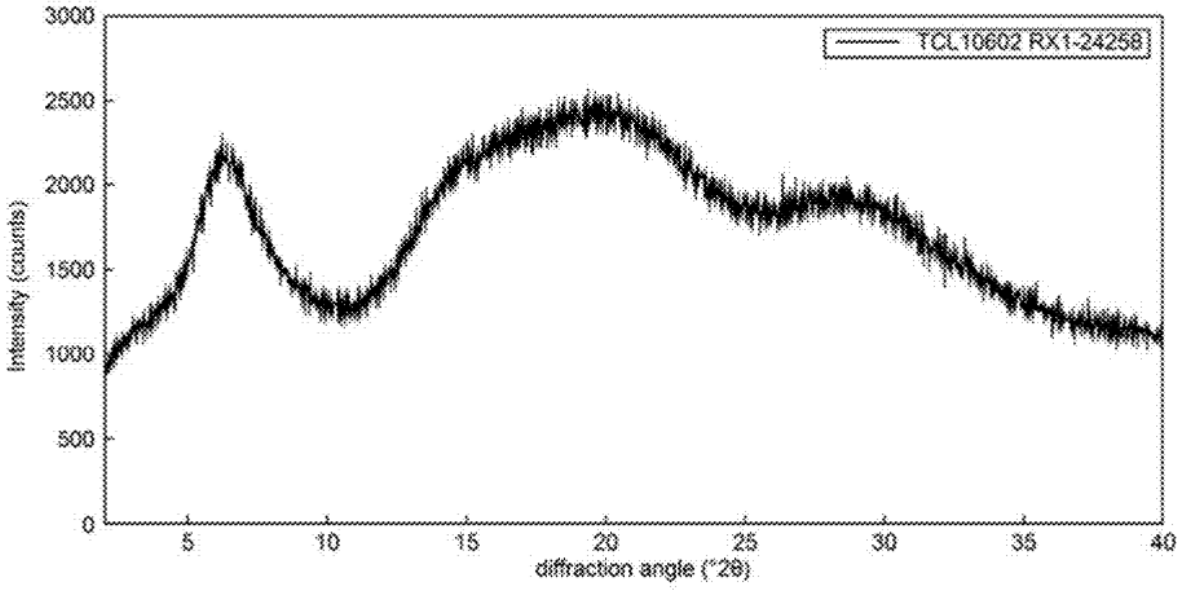
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product of claim 8,	
[20a] wherein the composition is amorphous.	The ’608 Publication discloses and/or renders obvious this limitation based on at least the following citations. *See, e.g.*: • ’608 Publication at Abstract A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water. • ’608 Publication at [0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium. • ’608 Publication at [0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi “The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State,” Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations. • ’608 Publication at [0012] Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%,

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	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.). • ’608 Publication at [0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, 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). • ’608 Publication at [0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection. • ’608 Publication at [0068], Fig. 5B FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

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	Fig. 5B  • ’608 Publication at [0069], Fig. 5C FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

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	Fig. 5C  • ’608 Publication at [0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. 1A-1F and the XRPD analysis shown in FIG. 5A-5D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to

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	embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG. • ’608 Publication at [0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at [0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. • ’608 Publication at [0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

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	• ’608 Publication at claim 1 1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium. • ’608 Publication at claim 16 16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual. To the extent the ’608 Publication does not expressly disclose this limitation, a person of ordinary skill in the art would have determined that this limitation is either inherent and/or obvious to one of ordinary skill in the art in view of the teachings of the ’608 Publication. Further, one of ordinary skill in the art would have been motivated to modify the ’608 Publication or combine it with any of the present prior art references found in Sun’s Invalidity Contentions and any supplements thereto and the relevant section charts for other prior art for the ’076 Patent in a manner that would result in the subject matter of this limitation given, at the very least, the person’s understanding of the state of the art, the problems addressed and solved in the prior art, and the teachings of the ’608 Publication.

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