FILE HISTORY

US 11,878,076

PATENT:	11,878,076
INVENTORS:	CHODAVARAPU BALA TRIPURA SUNDARI
	MANGALI THIRUPATHI
	SHUKLA JAY
	SHUKLA ANAND
	LAKKARAJU DASARADHI
TITLE:	Lyophilized compositions of phenobarbital sodium salt
APPLICATION NO:	US18100804A
FILED:	24 JAN 2023
ISSUED:	23 JAN 2024
COMPILED:	05 FEB 2025

Lyophilized compositions of phenobarbital sodium salt

Transaction History

Date	Transaction Description
01-24-2023	PTO-SB-69-Authorize EPO Access to Search Results
01-24-2023	Applicants have given acceptable permission for participating foreign
01-24-2023	Track 1 Request
01-24-2023	Petition Entered
01-24-2023	Entity Status Set To Undiscounted (Initial Default Setting or Status Change)
01-24-2023	Initial Exam Team nn
02-14-2023	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27
02-16-2023	Sent to Classification Contractor
02-16-2023	FITF set to YES - revise initial setting
02-16-2023	Patent Term Adjustment - Ready for Examination
02-17-2023	Mail Pre-Exam Notice
02-17-2023	Application Is Now Complete
02-17-2023	Filing Receipt
02-20-2023	Application Dispatched from OIPE
02-23-2023	Email Notification
03-14-2023	Record Petition Decision of Granted to Make Special
03-14-2023	Pet Dec Track 1 Grant
03-15-2023	Mail Pet Dec Track 1 Grant
03-15-2023	Track 1 Request Granted
03-15-2023	Mail-Record Petition Decision of Granted to Make Special
03-16-2023	Email Notification
03-16-2023	Email Notification
04-21-2023	Information Disclosure Statement (IDS) Filed
04-21-2023	Information Disclosure Statement (IDS) Filed
05-15-2023	Case Docketed to Examiner in GAU
05-24-2023	PG-Pub Issue Notification
05-25-2023	Application ready for PDX access by participating foreign offices
06-03-2023	Case Docketed to Examiner in GAU
06-16-2023	Non-Final Rejection
06-16-2023	Information Disclosure Statement considered
06-23-2023	Electronic Review
06-23-2023	Electronic Review
06-23-2023	Electronic Review
06-23-2023	Email Notification
06-23-2023	Mail Non-Final Rejection
09-07-2023	Electronic request for Examiner Interview
09-19-2023	Response after Non-Final Action
09-20-2023	Miscellaneous Incoming Letter
09-20-2023	Interview Summary - Applicant Initiated - Telephonic
09-20-2023	Interview Summary Record
09-25-2023	Email Notification
09-25-2023	Mail Examiner Interview Summary (PTOL - 413)
09-27-2023	Date Forwarded to Examiner
10-08-2023	Notice of Allowance Data Verification Completed
10-16-2023	Email Notification
10-16-2023	Mail Notice of Allowance
10-26-2023	PUB Other miscellaneous communication to applicant
10-30-2023	Email Notification
10-30-2023	Mail PUB other miscellaneous communication to applicant
11-03-2023	Amendment after Notice of Allowance (Rule 312)
11-07-2023	Pubs Case Remand to TC
11-08-2023	Corrected Notice of Allowability
11-14-2023	Email Notification

11-14-2023	Mailing Corrected Notice of Allowability
11-22-2023	Amendment after Notice of Allowance (Rule 312)
11-22-2023	Issue Fee Payment Verified
11-22-2023	Issue Fee Payment Received
12-01-2023	Pubs Case Remand to TC
12-05-2023	Response to Amendment under Rule 312
12-08-2023	Dispatch to FDC
12-08-2023	Application Is Considered Ready for Issue
12-11-2023	Pubs Case Remand to TC
12-11-2023	Email Notification
12-11-2023	Mail Response to 312 Amendment (PTO-271)
12-12-2023	Corrected Notice of Allowability
12-15-2023	Email Notification
12-15-2023	Mailing Corrected Notice of Allowability
01-03-2024	Issue Notification Mailed
01-04-2024	Email Notification
01-23-2024	Recordation of Patent Grant Mailed
01-23-2024	Email Notification
01-23-2024	Mail Patent eGrant Notification
01-23-2024	Patent eGrant Notification
01-23-2024	Recordation of Patent eGrant
01-23-2024	Patent Issue Date Used in PTA Calculation

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

CPC								
Symbol							Type	Version
A61K	/	9	/	19			F	2013-01-01
A61K	/	47	/	02			I	2013-01-01
A61K	/	31	/	515			I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	29 September 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20230929

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	9	/	19

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	29 September 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20230929

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	21	10	30												
2	22	11	31												
3	23	12	32												
4	24	13	33												
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6	26														
7	27														
8	28														
9	29														

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	29 September 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20230929

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	CARLOS A AZPURU	1617

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
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2	22	11	31												
3	23	13	32												
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8	28														
9	29														

Change(s) applied
to document,
/N.B.H./
11/20/2023

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	29 September 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20230929

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	CARLOS A AZPURU	1617

CPC								
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A61K	/	9	/	19			F	2013-01-01
A61K	/	47	/	02			I	2013-01-01
A61K	/	31	/	515			I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	20	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	12 December 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20231212

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	9	/	19

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	20	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	12 December 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20231212

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	21	10	30	19	39										
2	22	11	31	20	40										
3	23	13	32												
4	24	12	33												
5	25	14	34												
6	26	15	35												
7	27	16	36												
8	28	17	37												
9	29	18	38												

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	20	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	12 December 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20231212

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/100,804	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/15, A61K 9/19, A61K 9/0019	06/23/2023	CA
A61K 31/15, A61K 9/19, A61K 9/0019	09/29/2023	CA

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
inventor and assignee name search	06/23/2023	CA
Google Chrome	06/23/2023	CA
PE2E	06/23/2023	CA
Google Chrome	09/29/2023	CA
PE2E	09/29/2023	CA

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K 31/15	PE2E	09/29/2023	CA

Web Search History

date, time	web site	search string
6/16/2023 6:15:25 PM	Google	phenobarbital sodium powder anhydrous stable

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	224118	lyophilized AND (phenobarbital sodium)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
L2	160620	L1 AND powder	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
L3	126666	L2 AND ((storage stable) OR (shelf stable))	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:06 PM
L4	78293	L3 AND (lacks impurities)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:07 PM
L5	11911	L4 AND humidity	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L6	5731880	L AND temperature	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L7	11784	L5 AND temperature	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L8	6148	L7 AND (lyophilize OR (freeze dry?))	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:09 PM
L9	5831	L8 AND (dry OR drying)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:10 PM
L10	4678	L9 AND A61K 31/15.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L11	4678	L10 AND A61K 9/19.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L12	4678	L11 AND A61K 9/0019.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L13	3053	L12 AND pure	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L14	3031	L13 AND (drying step)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L15	2727	L14 AND primary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L16	2496	L15 AND secondary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	224118	lyophilized AND (phenobarbital sodium)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
L2	160620	L1 AND powder	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
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L4	78293	L3 AND (lacks impurities)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:07 PM
L5	11911	L4 AND humidity	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L6	5731880	L AND temperature	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
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L9	5831	L8 AND (dry OR drying)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:10 PM
L10	4678	L9 AND A61K 31/15.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L11	4678	L10 AND A61K 9/19.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L12	4678	L11 AND A61K 9/0019.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L13	3053	L12 AND pure	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L14	3031	L13 AND (drying step)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L15	2727	L14 AND primary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L16	2496	L15 AND secondary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L17	1442	L16 AND anhydrous	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:14 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
9/29/2023 12:07:36 PM	Google	phenobarbital sodium amorphous anhydrous stable

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	224118	lyophilized AND (phenobarbital sodium)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
L2	160620	L1 AND powder	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:05 PM
L3	126666	L2 AND ((storage stable) OR (shelf stable))	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:06 PM
L4	78293	L3 AND (lacks impurities)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:07 PM
L5	11911	L4 AND humidity	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L6	5731880	L AND temperature	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L7	11784	L5 AND temperature	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:08 PM
L8	6148	L7 AND (lyophilize OR (freeze dry?))	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:09 PM
L9	5831	L8 AND (dry OR drying)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:10 PM
L10	4678	L9 AND A61K 31/15.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L11	4678	L10 AND A61K 9/19.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:11 PM
L12	4678	L11 AND A61K 9/0019.ccls.	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L13	3053	L12 AND pure	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:12 PM
L14	3031	L13 AND (drying step)	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L15	2727	L14 AND primary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L16	2496	L15 AND secondary	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:13 PM
L17	1442	L16 AND anhydrous	(US-PGPUB; USPAT)	OR	ON	ON	2023/06/16 06:14 PM
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L19	3	L18 AND PEAU	(US-PGPUB; USPAT)	OR	ON	ON	2023/09/29 11:15 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

US011878076B2

(12) **United States Patent**
Chodavarapu et al.

(10) **Patent No.: US 11,878,076 B2**
(45) **Date of Patent: Jan. 23, 2024**

(54) **LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT**

(71) Applicant: **Nivagen Pharmaceuticals, Inc.**, Sacramento, CA (US)

(72) Inventors: **Bala Tripura Sundari Chodavarapu**, Davis, CA (US); **Thirupathi Mangali**, Sacramento, CA (US); **Jay Shukla**, Sacramento, CA (US); **Anand Shukla**, Denver, CO (US); **Dasaradhi Lakkaraju**, Sacramento, CA (US)

(73) Assignee: **NIVAGEN PHARMACEUTICALS, INC.**, Sacramento, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **18/100,804**

(22) Filed: **Jan. 24, 2023**

(65) **Prior Publication Data**

US 2023/0157959 A1 May 25, 2023

Related U.S. Application Data

(63) Continuation of application No. 17/854,914, filed on Jun. 30, 2022, which is a continuation-in-part of application No. 17/025,881, filed on Sep. 18, 2020, now Pat. No. 11,406,598.

(60) Provisional application No. 62/903,511, filed on Sep. 20, 2019.

(51) **Int. Cl.**

A61K 9/19	(2006.01)
A61K 47/02	(2006.01)
A61K 31/515	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 9/19*** (2013.01); ***A61K 31/515*** (2013.01); ***A61K 47/02*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/15; A61K 9/19; A61K 9/0019
See application file for complete search history.

(56) **References Cited**

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OTHER PUBLICATIONS

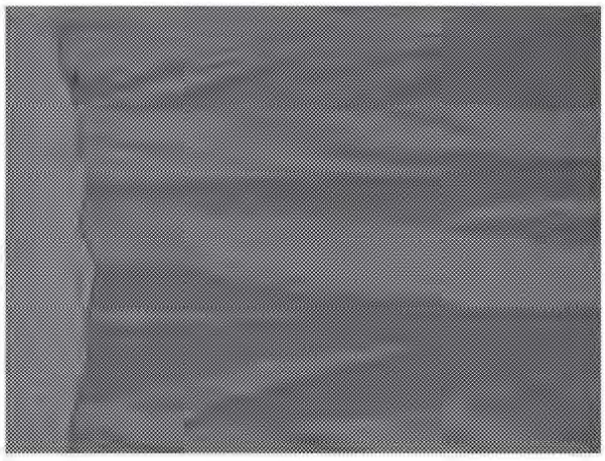
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Bardat et al., "Moisture Measurement: A New Method for Monitoring Freeze-drying Cycles," Journal of Parenteral Science & Technology, Nov.-Dec. 1993; 47(6):293-299.
(Continued)

Primary Examiner — Carlos A Azpuru
(74) *Attorney, Agent, or Firm* — Umberg Zipser LLP

(57) **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.

20 Claims, 39 Drawing Sheets



(56) **References Cited**

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Nahata et al., "Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection," American Journal of Hospital Pharmacy, Feb. 1986; 43:384-385.

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Staudt, "Phenobarbital in newborn infants: Overview," Monatsschr Kinderheilkd, Apr. 1984; 132(4):194-202. Abstract only.

* cited by examiner

Fig. 1A

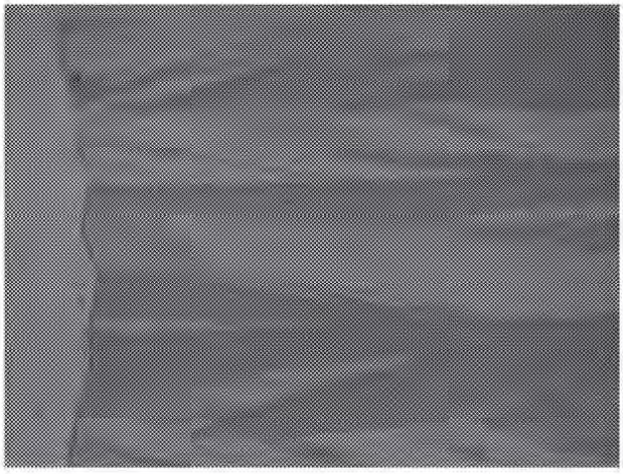


Fig. 1B

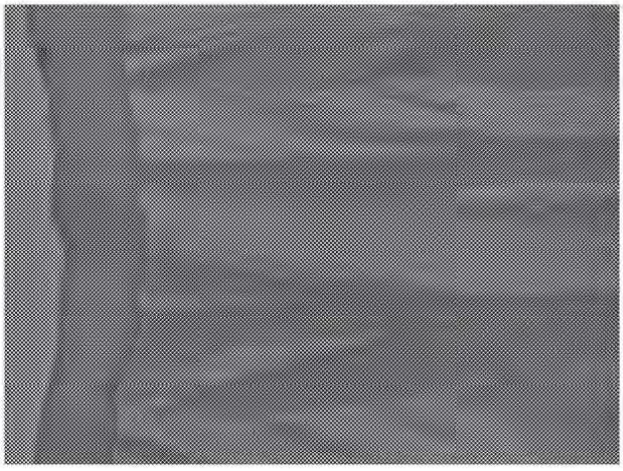


Fig. 1C

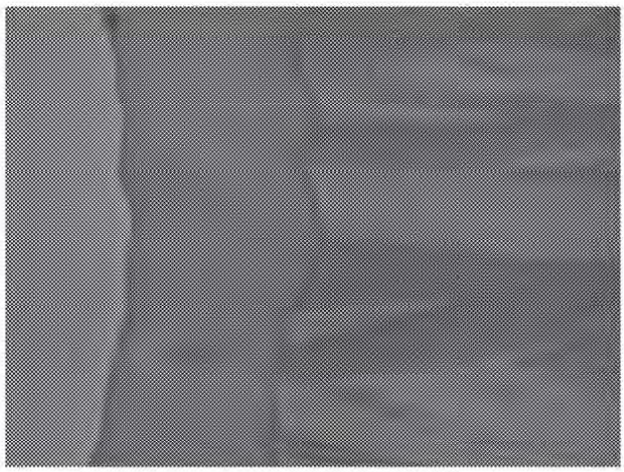


Fig. 1D

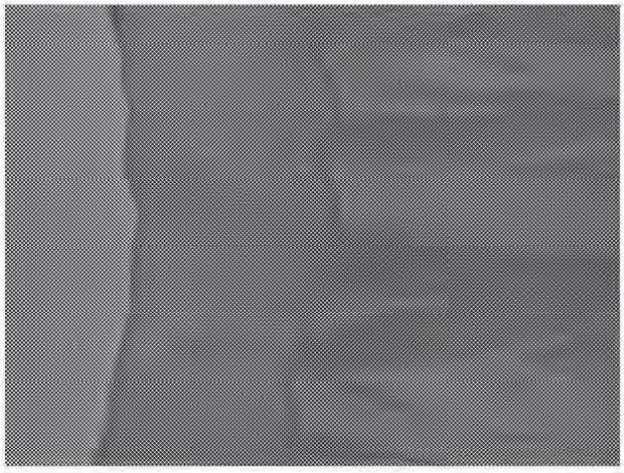


Fig. 1E

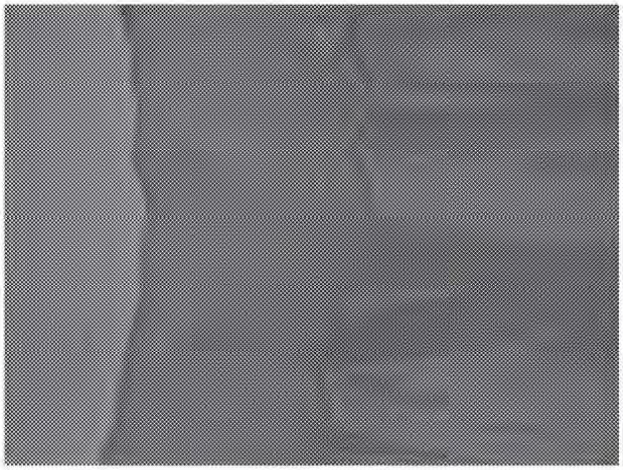


Fig. 1F

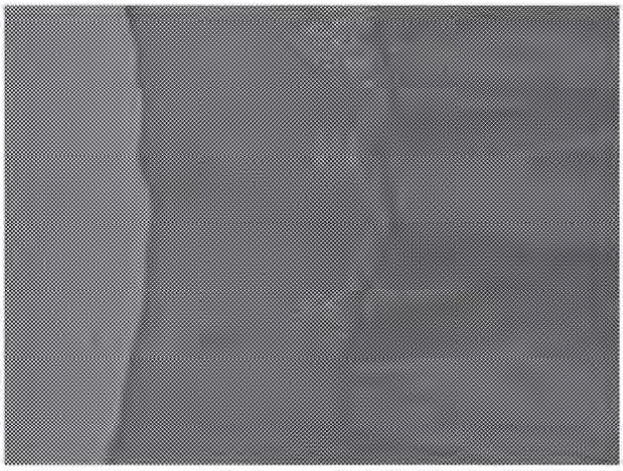


Fig. 2A

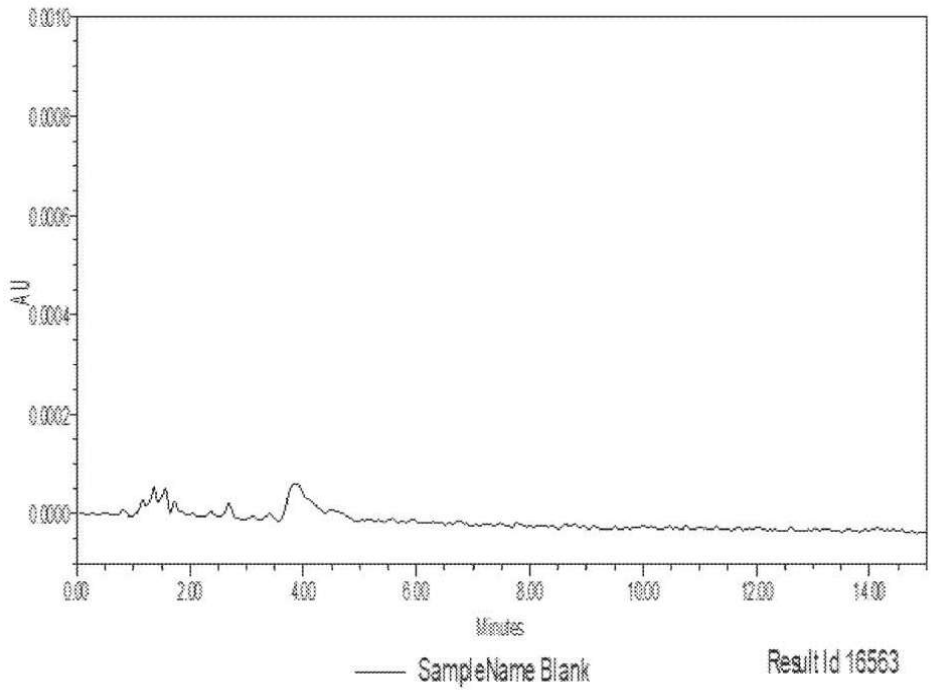
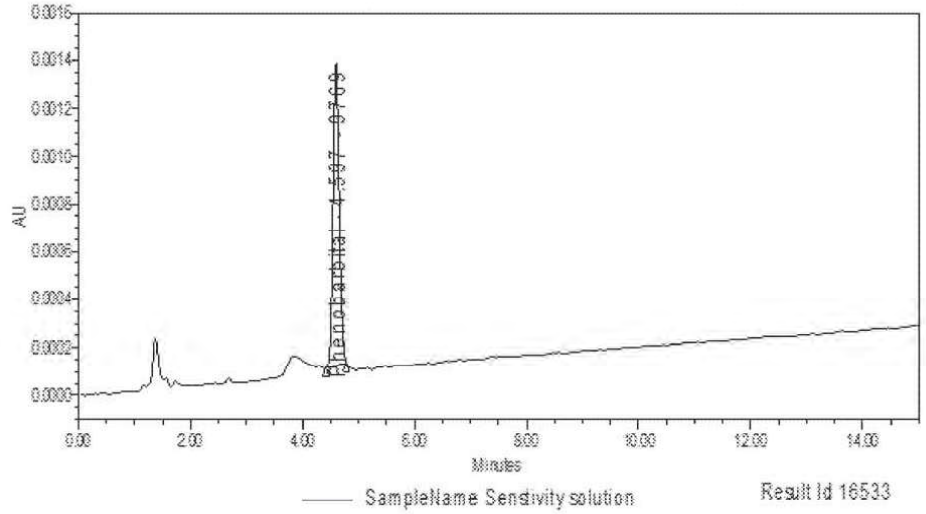
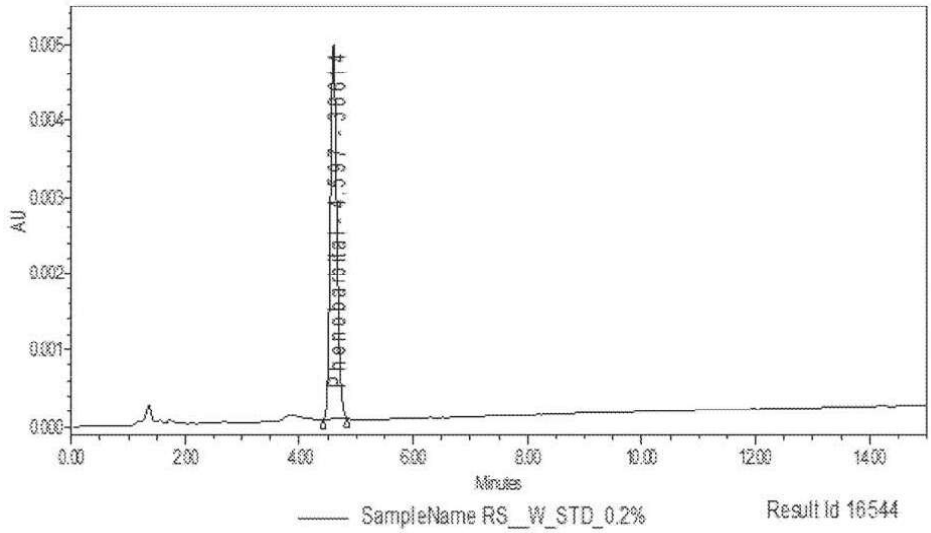

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Fig. 2B



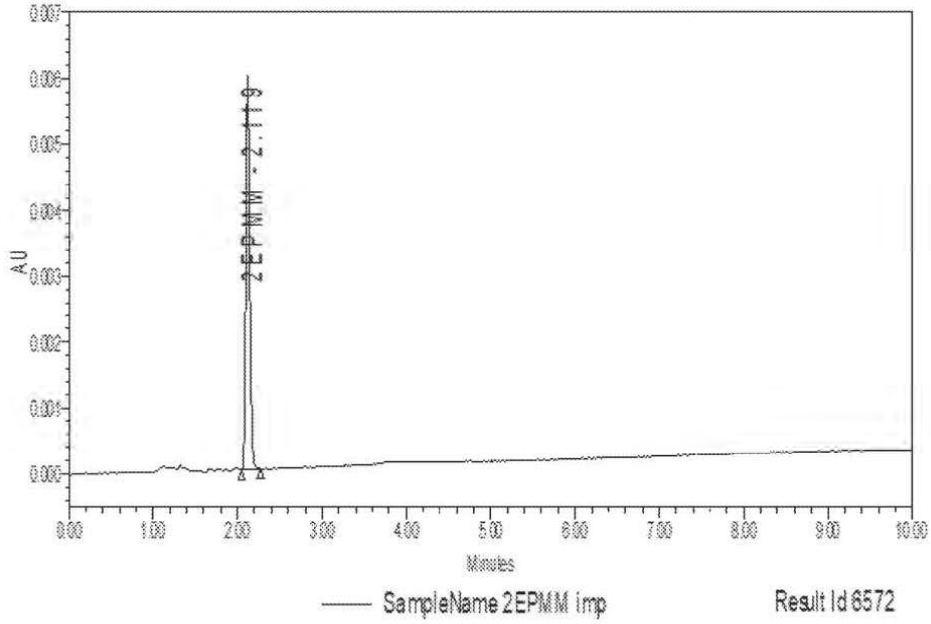
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7861.1	1.1

Fig. 2C



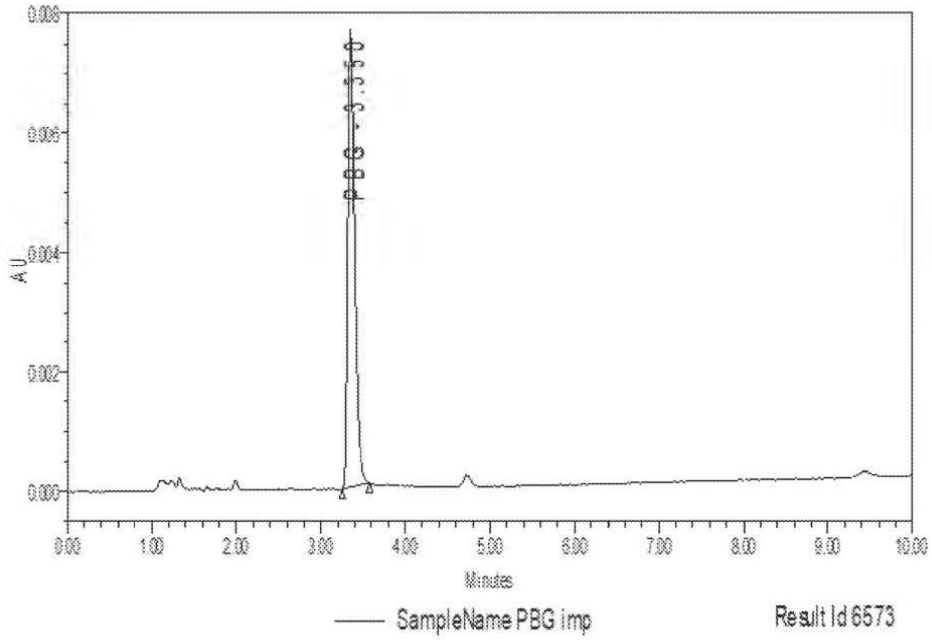
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	2EPMM	2.119	16797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	% Area	sn	USP Plate Count	USP Tailing	PurityA Angle	PurityA Threshold
1	PBG	3.350	41778	100.00	2090	66013	1.5	21.648	62.982

Fig. 2F

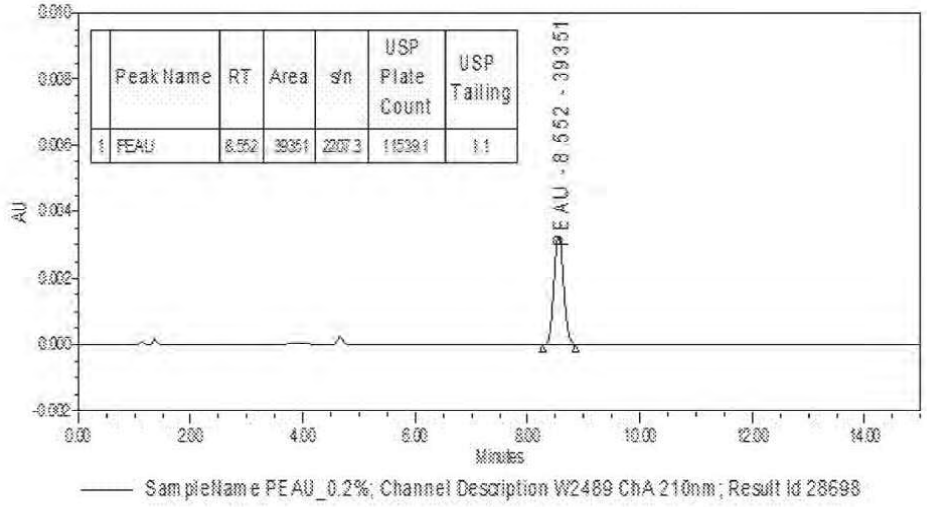

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RT
Area
s/n
USP Plate Count
USP Tailing
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Minutes
SampleName PEAU_0.2%; Channel Description W2489 ChA 210nm; Result Id 28698

Fig. 2G

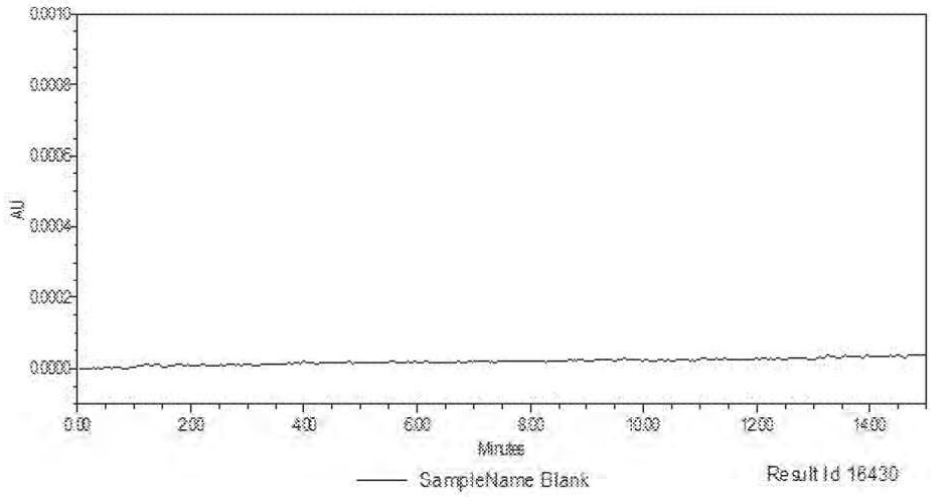
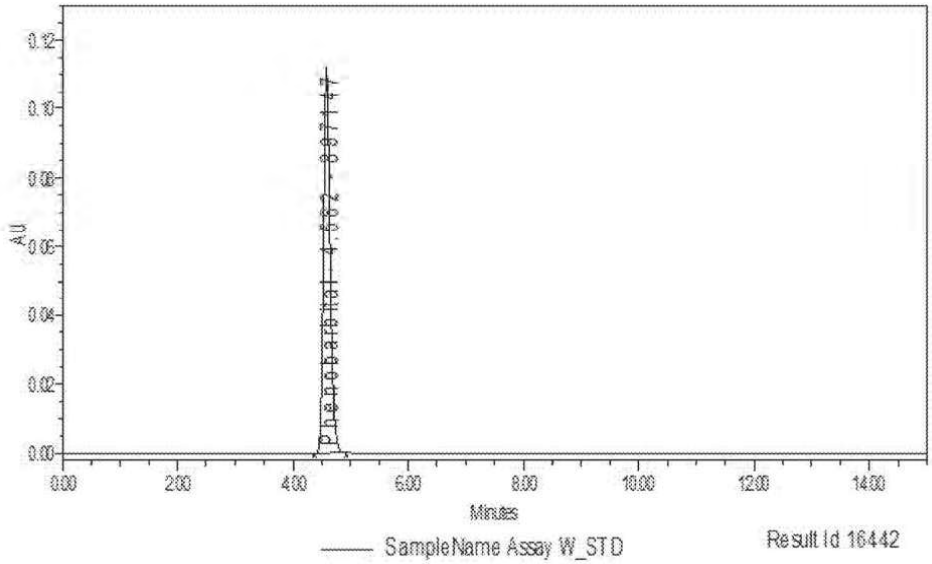
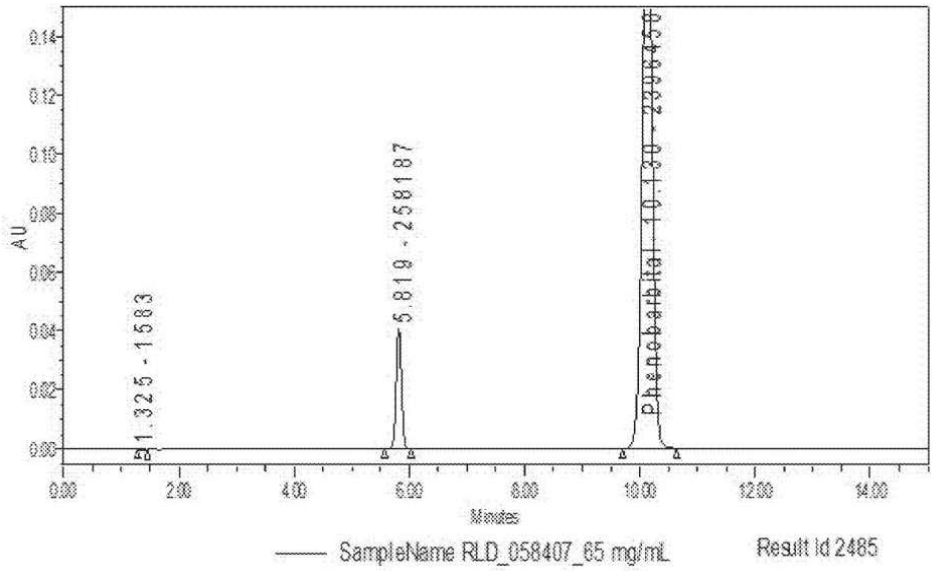

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Fig. 2H



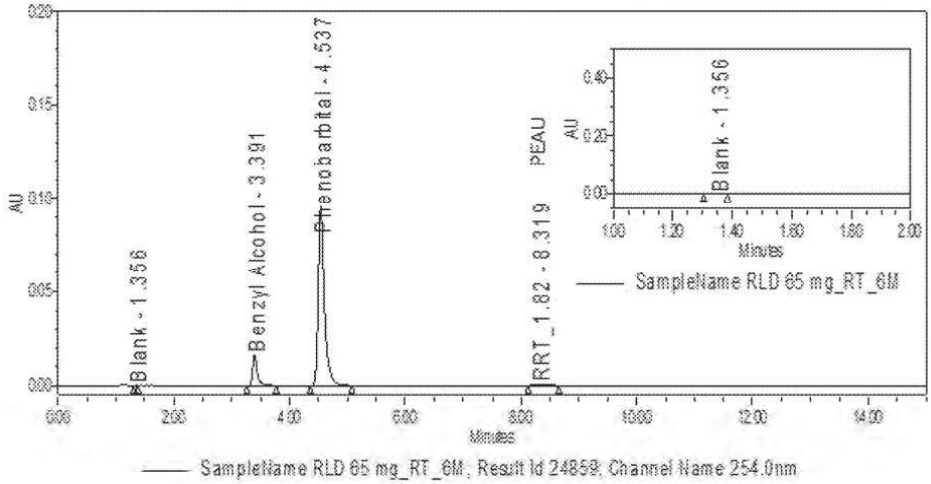
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



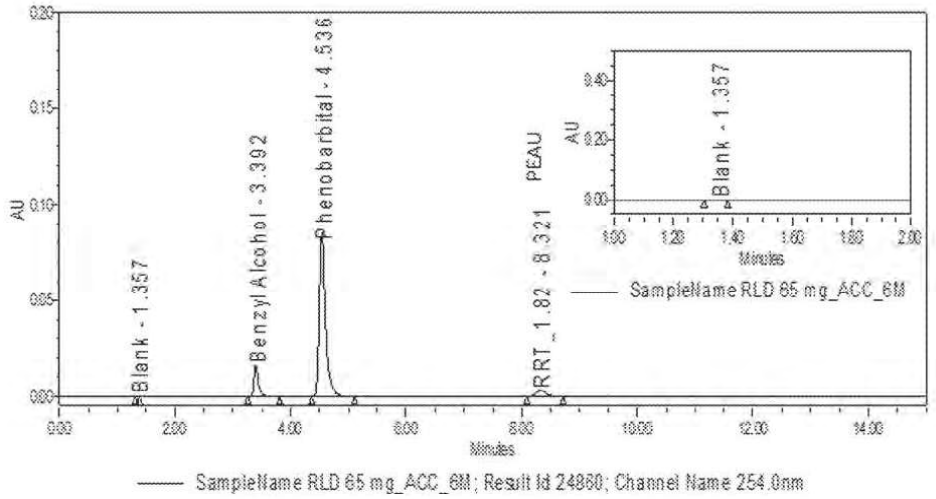
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	80.823	17.9	17534.1	1.0	112.1

Fig. 3B



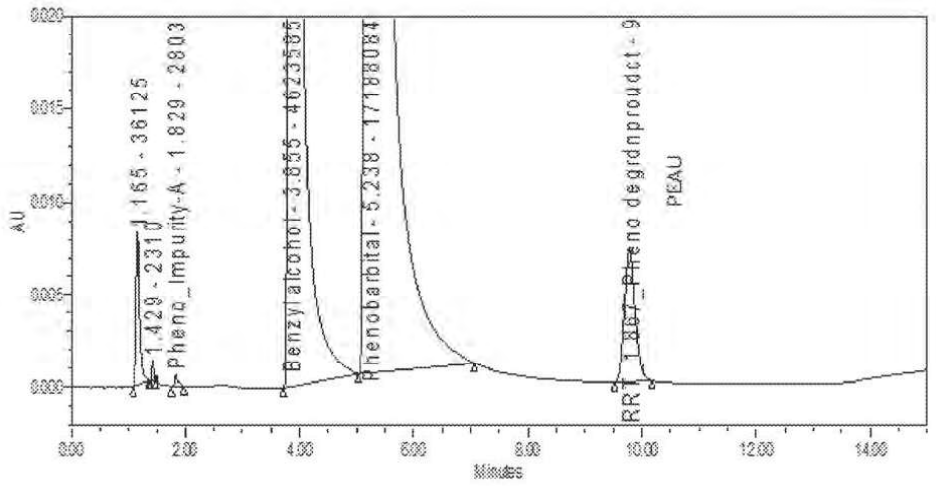
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



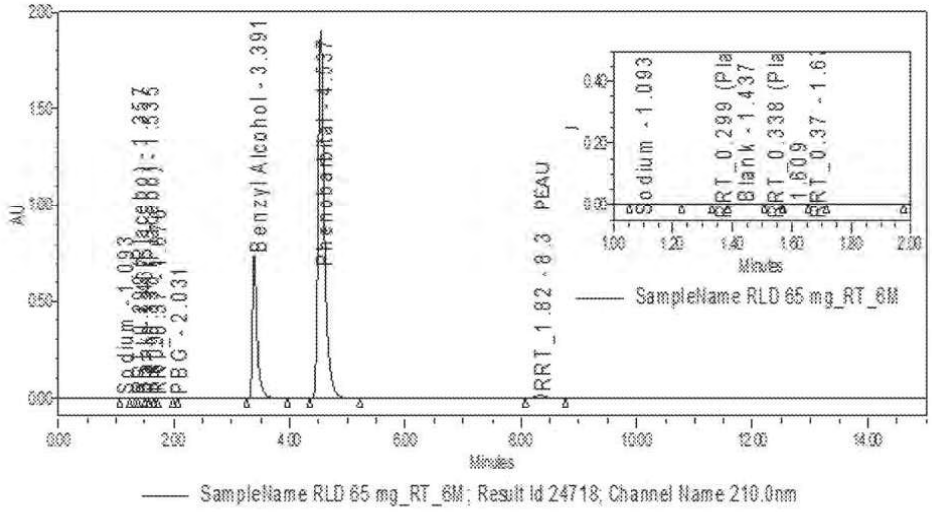
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627538	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

Fig. 3D



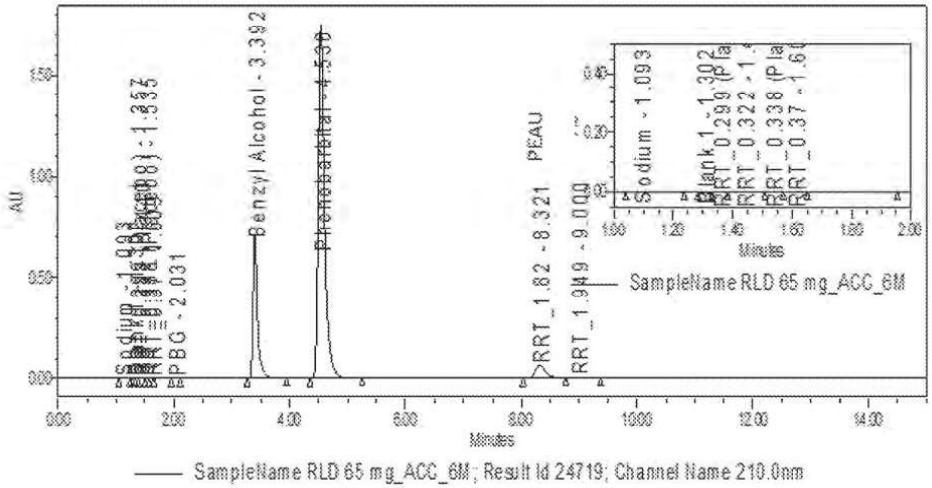
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4023585	21.07	17.1	390.1	12312.8	1.5
2	Pheno_impurityA	1.829	2803	0.01	5.2	0.3	7606.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1918.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92207	0.42	16.5	3.5	13191.9	1.2

Fig. 3E



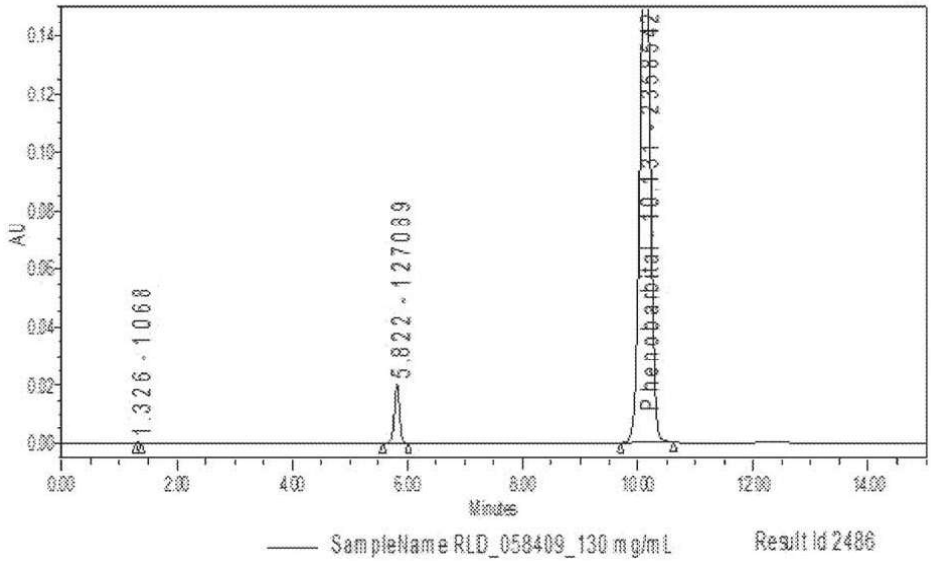
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



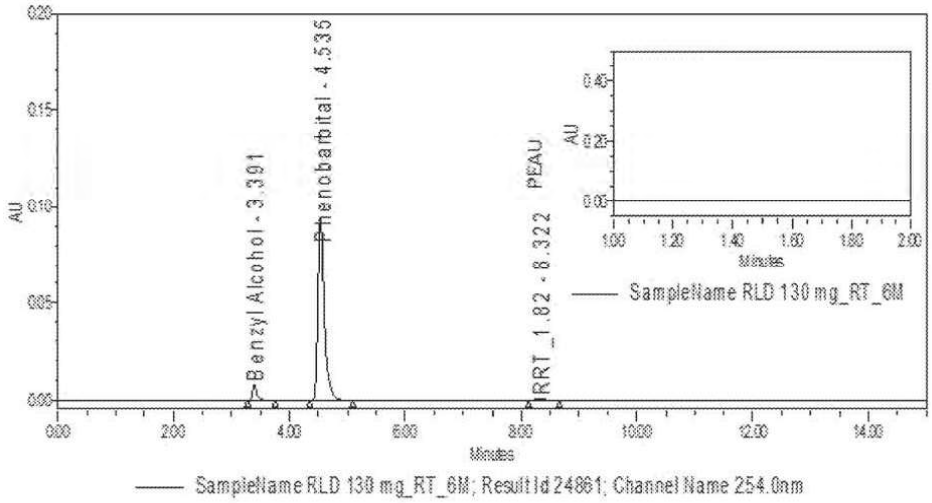
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



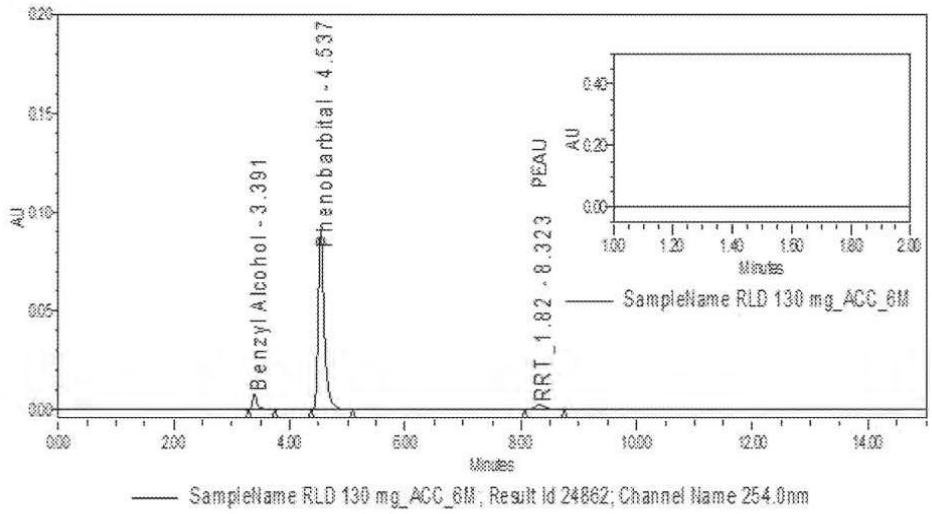
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



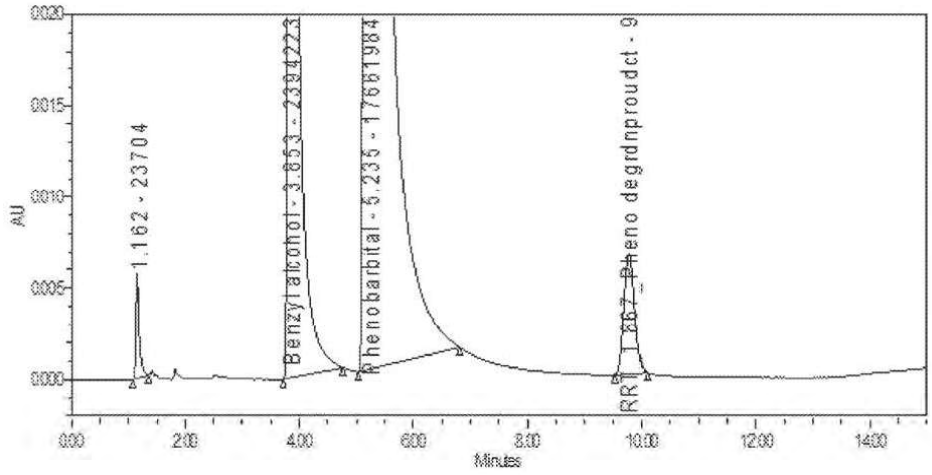
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



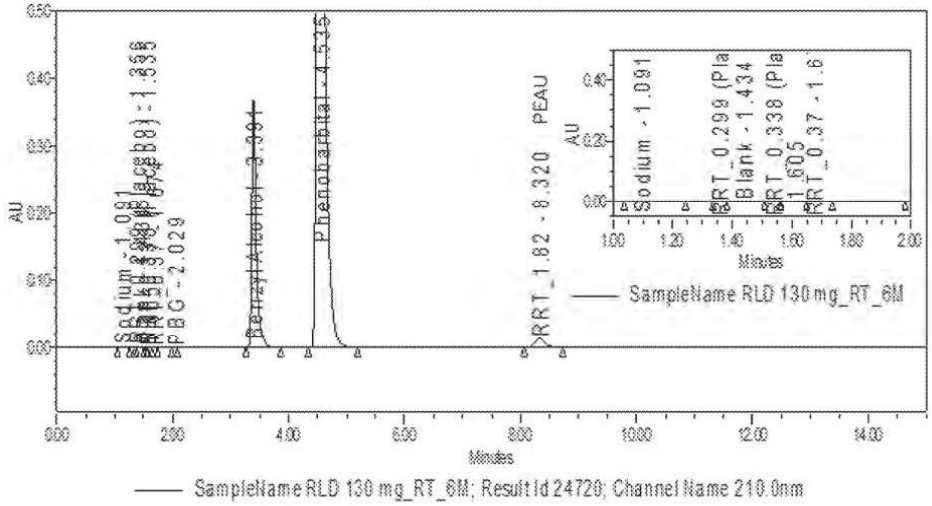
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



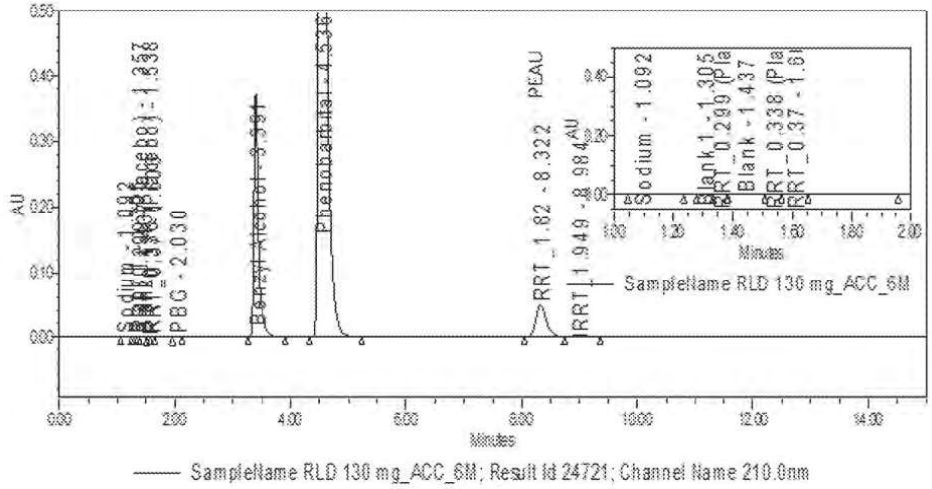
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3853	2394223	11.87	20.8	223.9	12438.0	1.5
2	Phenobarbital	5.235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Phenodegrdnproudct	9.776	83940	0.41	16.6	3.5	13512.7	1.1

Fig. 3K



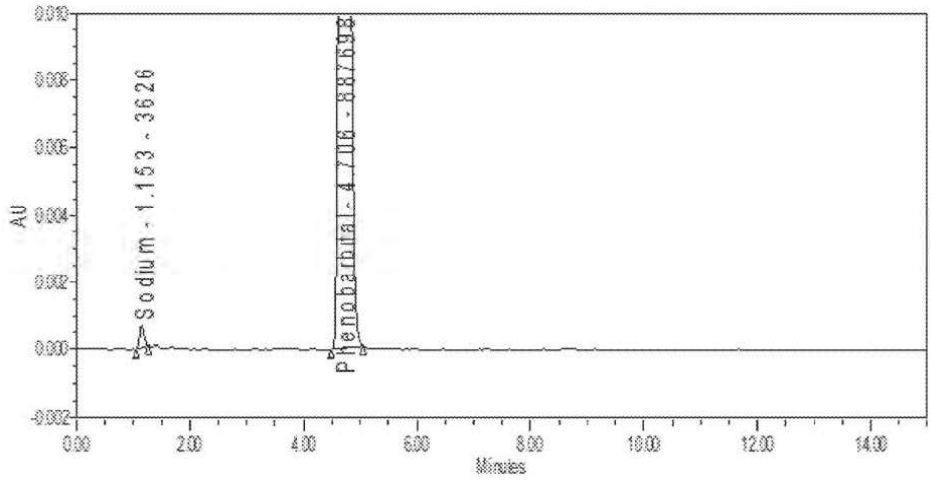
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.084	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

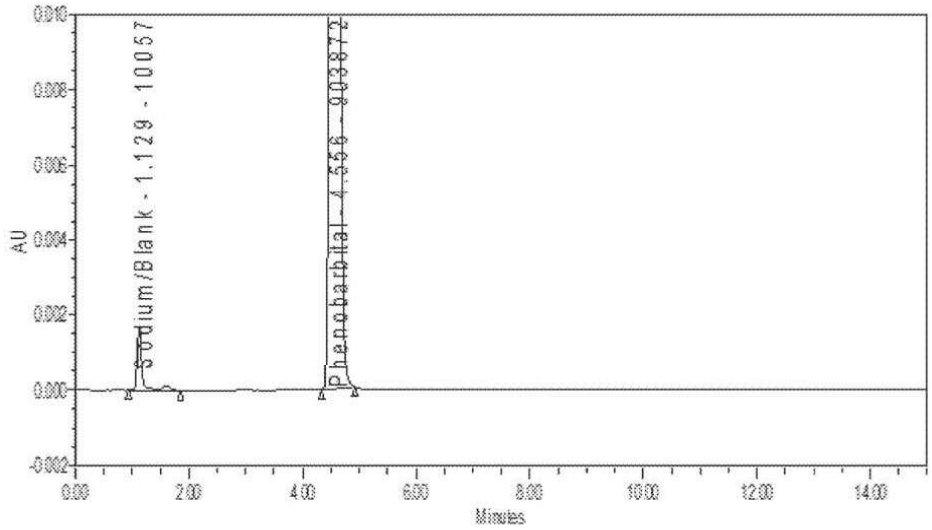
Fig. 4A



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

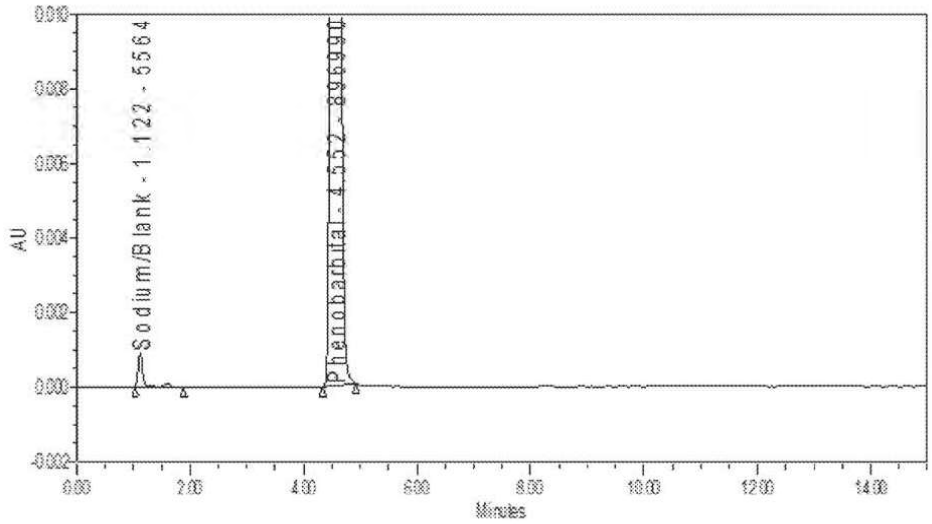
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887698	58.858	mg/mL	99.1	19.3	52343.5	7952.5	1.2
2	Sodium	1.153	3626					368.4	943.9	1.1

Fig. 4B



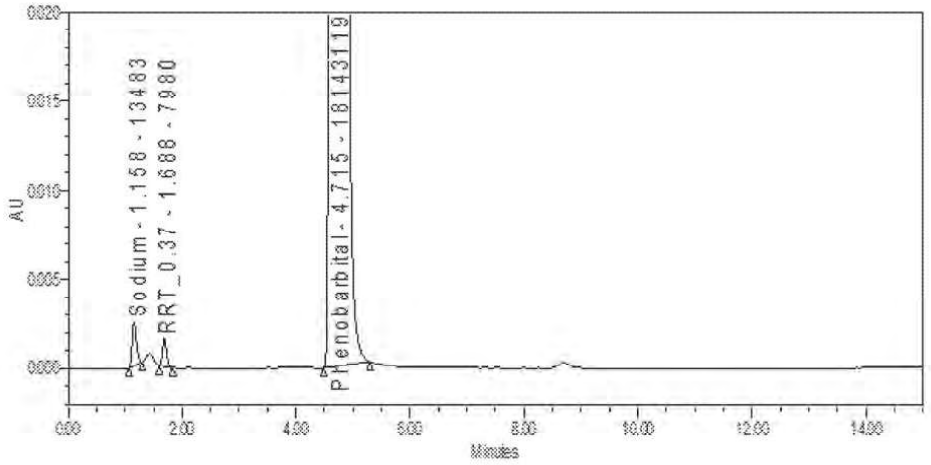
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.388	mg/mL	100.0	208	44822.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

Fig. 4C



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	89990	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1235.7	1.3

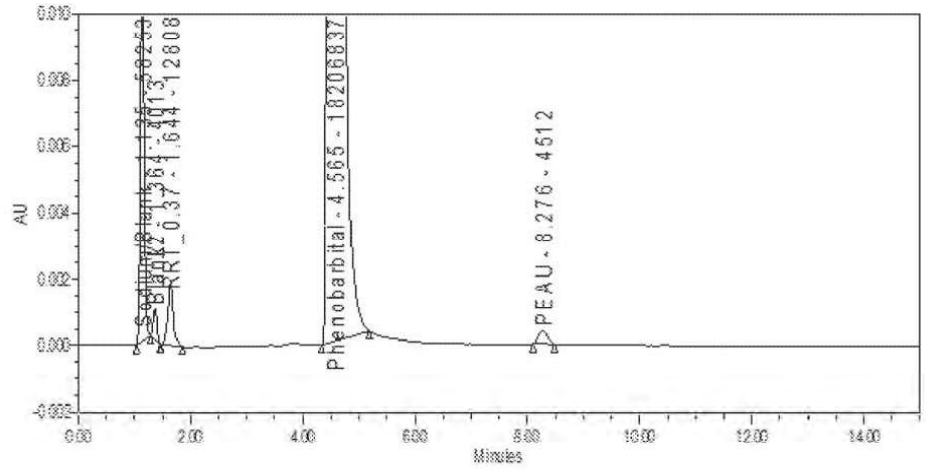
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.88	58.872	mg/mL	17.3	10731913	7804.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.026	mg/mL	37	772.4	28026	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1688.2	1.2

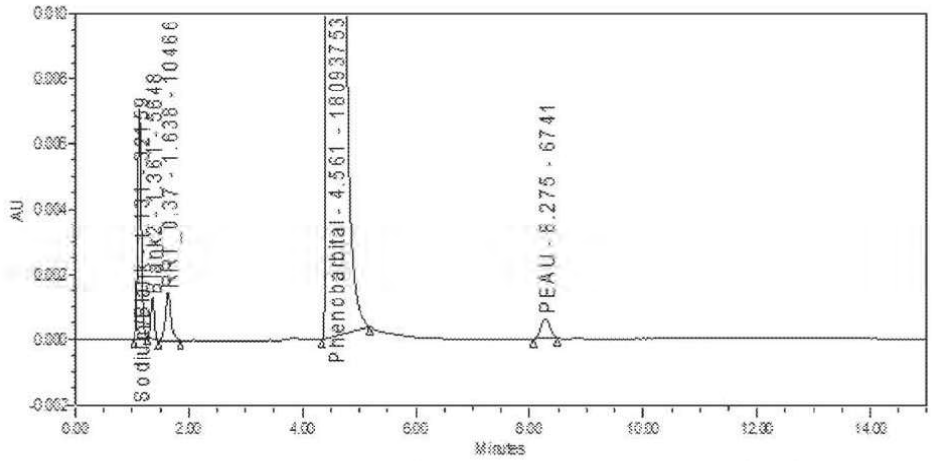
Fig. 4E



—— SampleName NPH1907_65mg_RT_6M ; Channel Description W2489 ChA 210nm; Result Id 31629

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4013	0.02			1.9	626.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12239.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	1619675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	SodiumBlank	1.135	58253	0.32	0.173	mg/mL		8406.1	1363.0	1.1

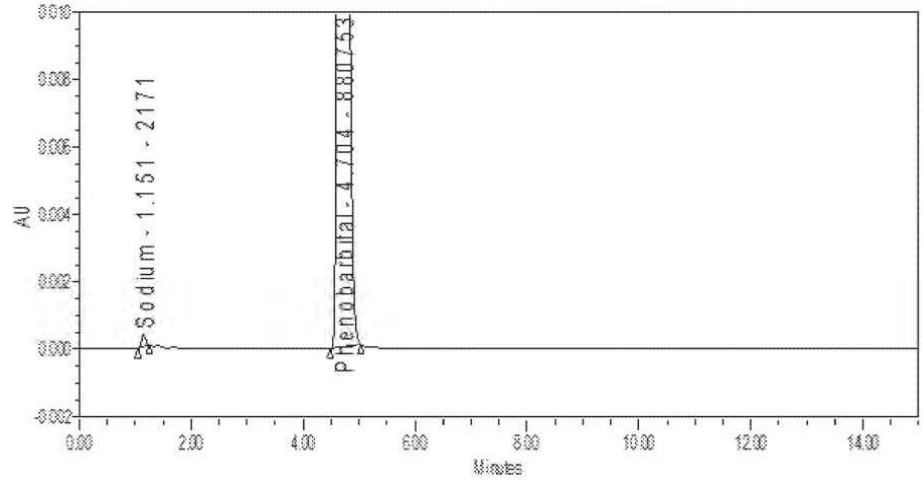
Fig. 4F



SampleName NPH1907_65mg_ACC_6M ; Channel Description W2489 ChA 210nm; Result Id 31632

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	5648	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11918.8	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1680108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1084.2	1482.5	1.1
5	SodiumBlank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

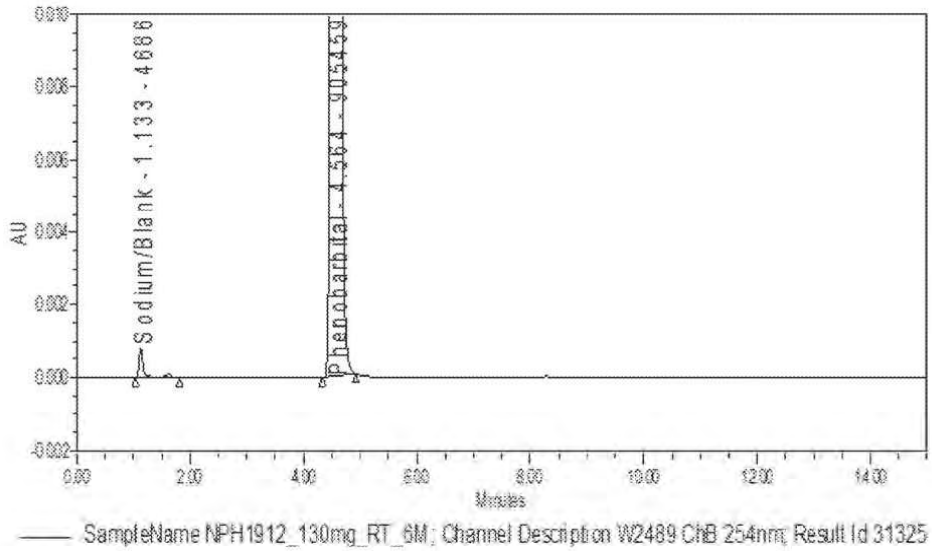
Fig. 4G



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

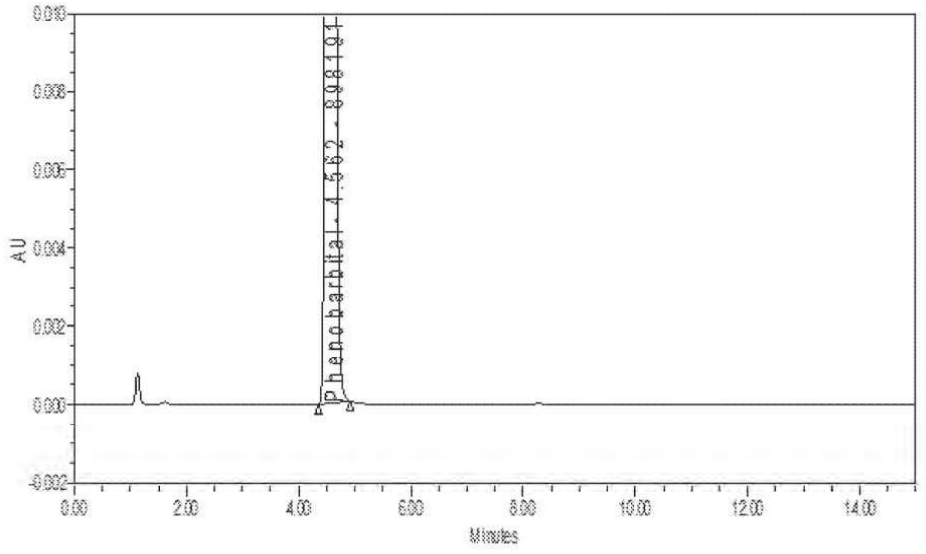
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	880753	116.796	mg/mL	98.3	19.3	40192.1	7866.8	1.2
2	Sodium	1.151	2171					148.3	959.0	1.0

Fig. 4H



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	55858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

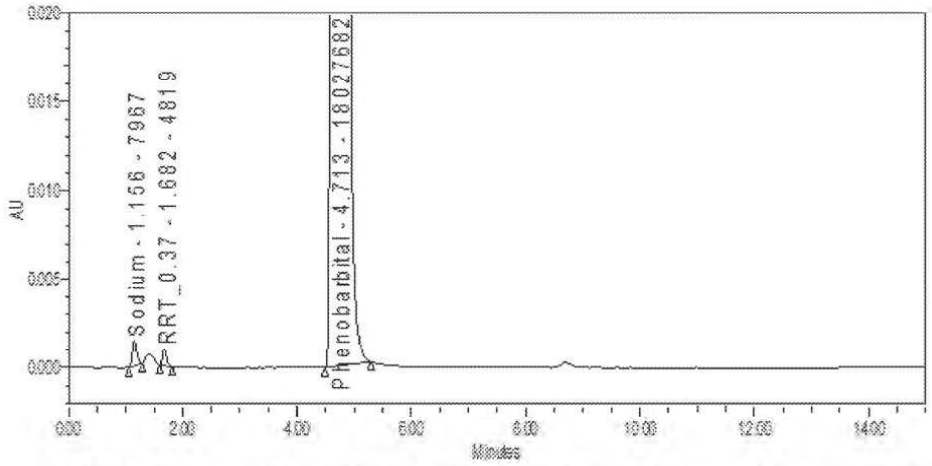
Fig. 4I



SampleName NPH1912_130mg_ACC_6M ; Channel Description W2489 ChB 254nm; Result Id 31328

	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898194	116.030	mg/mL	99.4	553756	8698.8	1.1

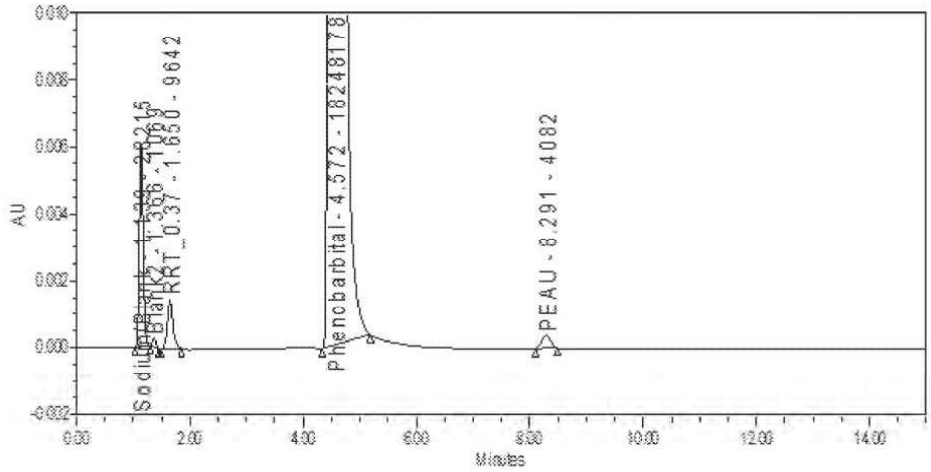
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14048

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.395	mg/mL	17.9	1001026.8	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	433.7	2491.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

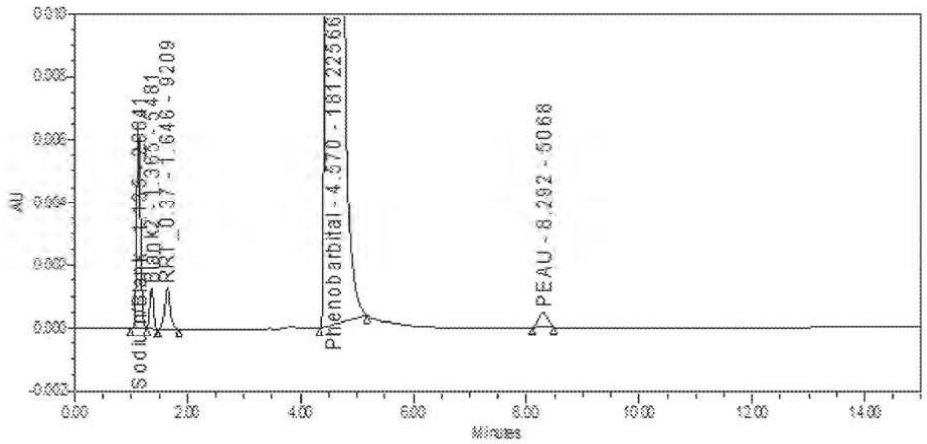
Fig. 4K



—— SampleName NPH1912_130mg_RT_6M; Channel Description W2489 ChA 210nm; Result Id 31637

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.6	1.0
3	Phenobarbital	4.572	18248178	99.76	106.187	mg/mL	15.9	1373502.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	2.0	832.7	1648.4	1.1
5	Sodium/Blank	1.139	28215	0.15	0.167	mg/mL		3438.2	1382.8	1.1

Fig. 4L



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChA 210nm; Result Id 31640

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.365	5481	0.03			1.9	887.2	2349.1	1.1
2	PEAU	8.292	5068	0.03	0.030	mg/mL	14.8	255.0	12120.6	1.0
3	Phenobarbital	4.570	18122566	99.73	107.442	mg/mL	15.1	13206538.2	6330.4	1.1
4	RRT_0.37	1.646	9209	0.05	0.055	mg/mL	1.8	725.3	1481.0	1.1
5	SodiumBlank	1.135	28641	0.16	0.171	mg/mL		3440.5	1382.6	1.1

Fig. 5A

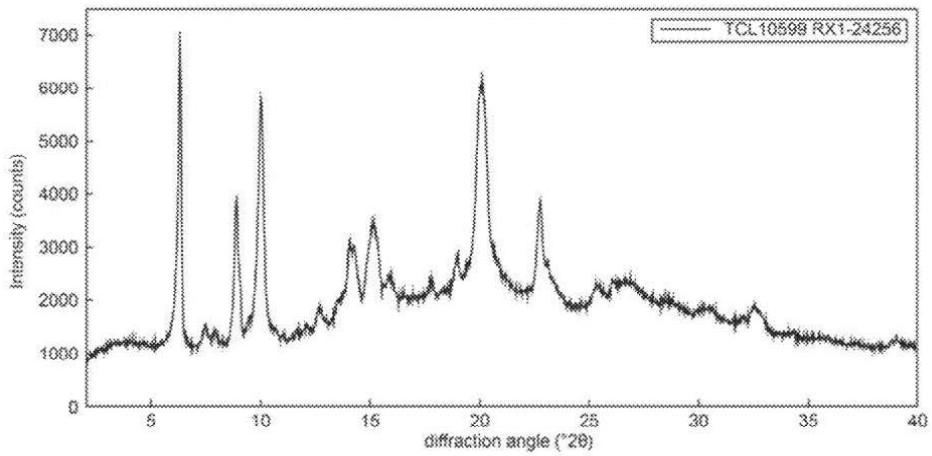

TCL10599 RX1-24256
Intensity (counts)
diffraction angle (°2θ)
0
1000
2000
3000
4000
5000
6000
7000
5
10
15
20
25
30
35
40

Fig. 5B

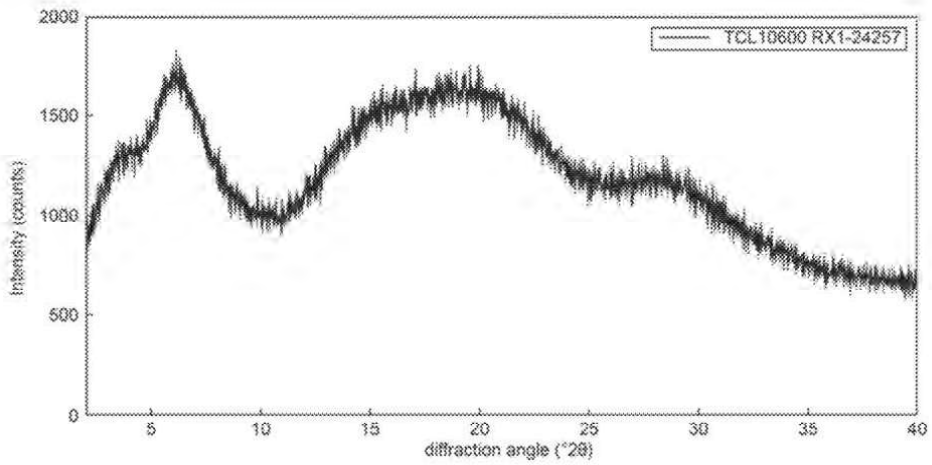

TCL10600 RX1-24257
Intensity (counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5C

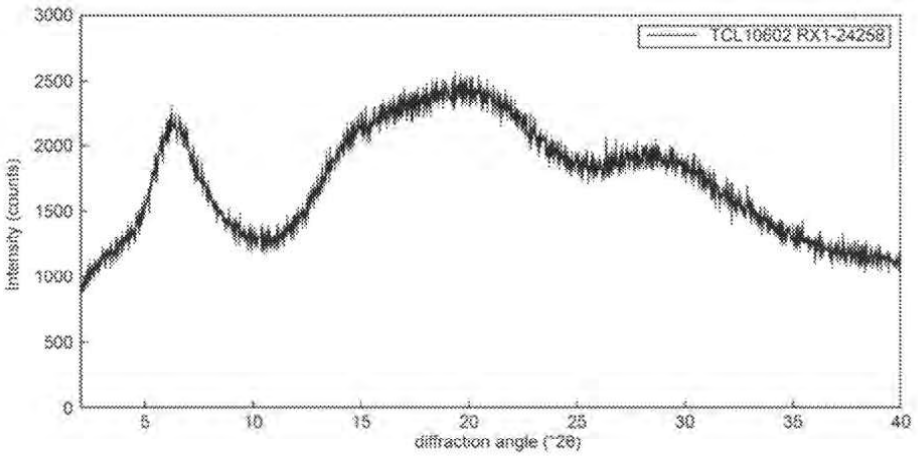
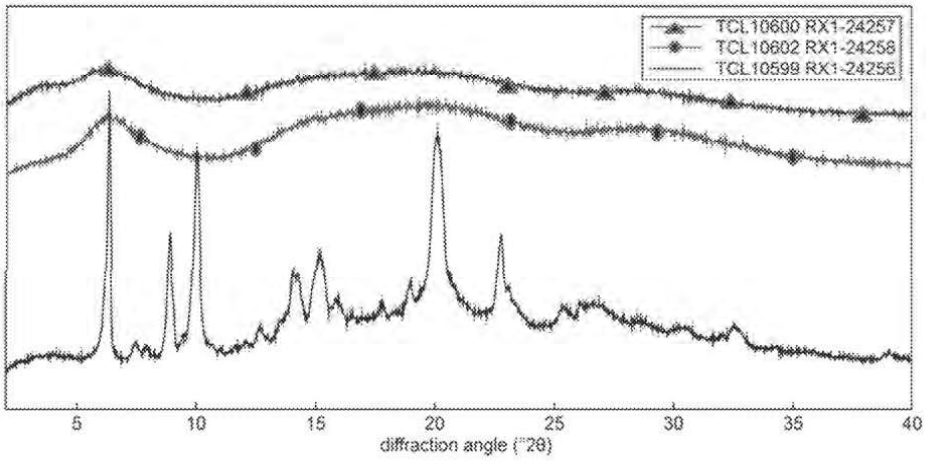

TCL10602 RX1-24268
Intensity (counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5D


TCL10600 RX1-24257
TCL10602 RX1-24258
TCL10599 RX1-24256
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT

RELATED APPLICATIONS

This application is a continuation application of our co-pending U.S. application with the Ser. No. 17/854,914, filed Jun. 30, 2022, which is a continuation-in-part application of our U.S. application with the Ser. No. 17/025,881, filed Sep. 18, 2020, now U.S. Pat. No. 11,406,598, which claims the benefit of U.S. Provisional Patent Application No. 62/903,511, filed on Sep. 20, 2019, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

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.

BACKGROUND OF THE INVENTION

The background description includes information that may be useful in understanding the present disclosure. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic. Phenobarbital Sodium is typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent. For example, WO 2017/085687 to Parker et al. discloses a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol.

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.

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.

In addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (e.g., Phenobarbital Sodium for Injection USP, 65 mg/mL or130 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.

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.

SUMMARY

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.

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.

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.).

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.

In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

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).

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.

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).

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.

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.

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 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.

In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

For adjusting the pH of the Phenobarbital Sodium solution, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution 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).

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.

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.

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.

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.

Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium.

Various objects, features, aspects, and advantages will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1**A is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −50° C., as indicated.

FIG. **1**B is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −45.5° C. as indicated.

FIG. **1**C is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −40.0° C. as indicated.

FIG. **1**D is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −39.6° C. as indicated.

FIG. **1**E is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −39.2° C. as indicated.

FIG. **1**F is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −38.8° C. as indicated.

FIG. **2**A is a chromatogram from an injection of a "blank solution" for assay by high performance liquid chromatography (HPLC) at a detection wavelength of 210 nanometers (nm), as described herein.

FIG. **2**B is a chromatogram from an injection of the "Sensitivity solution" of Phenobarbital for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**C is a chromatogram from an injection of a "related substance" (RS) working standard at 0.2% impurity level) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**D is a chromatogram from an injection of 2-ethyl-2-phenylmalonamide (2EPMM) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**E is a chromatogram from an injection of alpha-phenylbutyrylguanidine (PBG) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**F is a chromatogram from an injection of phenylethylacetylurea (PEAU) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**G is a chromatogram from an injection of a "blank solution" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **2**H is a chromatogram from an injection of an "assay working standard" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**A is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**B is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**C is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**D is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**E is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**F is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**G is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**H is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**I is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**J is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**K is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**L is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **4**A is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**B is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. 4C is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. 4D is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 4E is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 4F is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 4G is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. 4H is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. 4I is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. 4J is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 4K is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 4L is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. 5A is an X-ray powder diffraction (XRPD) pattern of Phenobarbital Sodium Grade P

FIG. 5B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

FIG. 5C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

FIG. 5D is a stack plot of the XRPD patterns of FIGS. 5A, 5B, and 5C.

DETAILED DESCRIPTION

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).

The Phenobarbital Sodium composition as described herein refers to Phenobarbital Sodium having an IUPAC (International Union of Pure and Applied Chemistry) name of sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$.

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.

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 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 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.

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 (O_2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N_2) 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.

The addition of the Phenobarbital Sodium solid to the water (e.g., deionized nitrogen sparged water cooled to 2 to 8° C.) may be carried out using any suitable mixing. Preferably, the water (e.g., Water for Injection) is first added to a glass/stainless steel container for nitrogen sparging and cooling, and this prepped water remains in the glass/stainless steel container or a measured amount is transferred to a preferably weighed glass container/stainless steel container and the Phenobarbital Sodium solid is added thereto. For mixing, any suitable mixing may be used. For example, a magnetic stir bar may be added to the glass/stainless steel container. Upon addition of the Phenobarbital Sodium solid to the water, the mixture is stirred.

An additional consideration for stability of the Phenobarbital Sodium is maintaining a pH between 9.2 and 10.2 in the bulk solution of Phenobarbital Sodium. After dissolution of the Phenobarbital Sodium solid in the water, the pH is adjusted to within this range of 9.2 and 10.2. Accordingly, the pH of the water solubilized Phenobarbital Sodium is first measured upon dissolution. If the pH is higher than 10.2 or lower than 9.2, the pH is adjusted. For example, if necessary, the pH may be lowered to or between 9.2 and 10.2 using Hydrochloric acid (HCl) and the pH may be increased to or between 9.2 and 10.2 using Sodium Hydroxide (NaOH).

Following the pH measurement and any adjustment, the Phenobarbital Sodium solution is preferably filtered to remove any foreign particles. For example, the Phenobarbital Sodium solution may be filtered using a 0.2 μm (or 0.22 μm) membrane filter. For example, the membrane filter may be polyvinylidene difluoride (PVDF) or any other compatible filter membranes such as Polyethersulfone (PES) filter.

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.

In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum.

Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium.

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.

In one embodiment, the water is Water for Injection.

In another embodiment the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.

In another embodiment, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.

In another embodiment, the water is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

In another embodiment, the adjusting includes measuring the pH of the Phenobarbital Sodium solution, and if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

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).

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).

In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylma-

lonamide (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).

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).

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.

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.

In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing.

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.

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.

In another embodiment, the individual suffers from epilepsy.

In another embodiment, the individual is a newborn suffering from neonatal epilepsy.

In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

In another embodiment, the administering includes intramuscular injection or intravenous injection.

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. **5**B-**5**C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade PAPI shown comparatively in FIG. **5**D. 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.

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. **2**A-**2**H, **3**A-**3**L, and **4**A-**4**L.

TABLE 1

Formulation Details

		Dosage form	
Components	Chemical name	Liquid mg/mL	Lyophilized 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

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. **3**A-**3**F, FIGS. **4**A-**4**F), 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. **3**G-**3**L, FIGS. **4**G-**4**L). 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).

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

Notably, the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration.

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-NPH1913)					
	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

TABLE 3-continued

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
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

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.

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.

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.

EXAMPLES

Lyophilization Microscopy. Lyophilization microscopy (FIGS. **1A-1F**) was performed using a Leica DM LP microscope equipped with a Linkam FDCS196 stage, TMS93 controller, vacuum pump, LNP unit, and a Spot Insight color camera. A 20×, 040 N.A. objective was used with crossed polarizers and a first order red compensator to view sample. Images were acquired using Spot Advanced software (v.4.5.9).

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.

HPLC Assays. High Performance Liquid Chromatography (HPLC) was used to assay Phenobarbital Sodium standards and sample solutions as disclosed herein (e.g., Tables

2, 3, FIGS. 2A-2H, 3A-3L, and 4A-4L). Both Ultra High-Performance Liquid Chromatographic system (UHPLC) and High-Performance Liquid Chromatographic system (HPLC) (ThermoFisher/Waters) were used together with Data Acquisition Software (Empower 3), equipped with UV and Photodiode Array Detector (UV and PDA), column thermostat and auto sampler compartments or equivalent HPLC system and software.

An exemplary HPLC assay protocol is provided in the following:

Instruments/Apparatus: HPLC with UV detector/PDA Detector, Analytical balance, Sonicator, Volumetric flasks, Beakers, Pipettes.

Reagents, Solvents, Standards: Phenobarbital Reference Standard, Deionized water/Water for Injection, Potassium Monobasic Phosphate, Acetonitrile.

Preparation of Mobile Phase Solutions: Potassium phosphate monobasic (7 mM) and Acetonitrile (70:30) pH 4.5-6.5; Diluent: Mobile phase as a diluent.

Wash Solvent: Water: Acetonitrile (70:30)

CHROMATOGRAPHIC CONDITIONS: The liquid chromatography equipped with a

Parameters	Conditions
Column	L7 packaging column, 150 × 4.6 mm, Particle Size: 5 µm or equivalent
Flow rate	0.9-1.2 mL/min.
Detection Wavelength	254 ± 2 nm for assay and 210 ± 2 nm for Related Substances
Injection volume	10 µL
Run time	15 Minutes
Column Oven Temperature	30° C.
Sampler Cooler Temperature	25° C.
Retention Time	About 5 minutes for Phenobarbital
Pump Mode	Isocratic

UV and PDA detector, an injector and a data processor is operated as follows:

Phenobarbital Assay Standard Solution: 0.2 mg/mL to 0.8 mg/mL in diluent; Phenobarbital Related Substances Standard Solution: 0.26 µg/mL to 15.6 µg/mL in diluent; Phenobarbital Related Substances resolution standard solution: 0.475 mg/mL Phenobarbital and about 1µg/mL for related substances (2-Ethyl-2-Phenyl malonamide, monohydrate (2EPMM), Phenylbutyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) in diluent; Phenobarbital Sodium Sample Solution for Assay: 0.26 mg/mL to 0.78 mg/mL in diluent

Phenobarbital Sodium related Substances sample solution: 0.52 mg/mL of Phenobarbital Sodium and related substances 2-Ethyl-2-Phenylmalonamide, monohydrate (2EPMM), Phenyl butyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) and any unspecified degradation products at 0.26 µg/mL to 13.2 µg/mL

SYSTEM SUITABILITY REQUIREMENTS: The relative standard deviation of Phenobarbital peak from Six replication injections of related substances standard should not be more than 6.0%. The related standard deviation of Phenobarbital peak from five replicate injections in assay standard solution should not be more than 2.0%. Tailing factor for the Phenobarbital is not more than 2.0. USP Plate count for the Phenobarbital is not less than 2500. The S/N Ratio of the Sensitivity Standard Solution is NLT 10 for related substance test. The resolution between Phenobarbital peak and nearest impurity peak is NLT 1.5

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.

	NPH2031 A (Bulk Solution at 100 mg · mL Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031 A (Bulk Solution at 100 mg · mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C. Fill Volume: 2.1 mL	
Ingredients	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	20	200	20	200
Sodium Chloride	NA	NA	9	90
WFI/DI Water	qs	qs	qs	qs

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

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

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
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
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)	NMT 0.2%	BQL	ND	BQL
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27

TABLE 8-continued

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

			Reconstituted Solution Stability after 20 hrs	
Test	Specification	Initial	2-8° C.	RT
Total degradation products	NMT 1.5%	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

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

TABLE 9

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

			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

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
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
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

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 Clear Glass Vial: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal.
API: Phenobarbital Sodium, USP Grade P
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	1 Month		3 Months		6 Months	
		DOA:	DOA: Mar. 23, 2020		DOA: May 20, 2020		DOA: Sep. 4, 2020	
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6
% 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

TABLE 10-continued

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 Clear Glass Vial: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal.
API: Phenobarbital Sodium, USP Grade P
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
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 11

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

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

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

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 Date Initiated: Jun. 9, 2020 API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:, Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203 Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay Phenobarbital Sodium	90.0-105.0	100.1	98.1	101.0
Related Substances (% Area)	NMT 0.2%	ND	ND	ND
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05

TABLE 12-continued

Product Name Phenobarbital Sodium for Injection USP, 200 mg/vial Batch#NPH2031A Fill Volume: 2.1 mL Date Manufactured: Jun. 3, 2020 Vial Make 10 mL Tubular Serum Bottle clear Date Initiated: Jun. 9, 2020 API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:, Stopper Used 20 mm Igloo Bromobutyl Lyophilization Rubber stopper Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal, 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
Total degradation products	NMT 1.5%	BQL	0.06	0.05
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051- 84 to 122	

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

TABLE 13

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

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

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

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)	≥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

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)
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)

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 Fill Volume: 1.0 mL Date Manufactured: Sep. 25, 2019
Vial Make 5 mL Clear Untreated 5 mL Clear Treated Date Initiated: Sep. 30, 2019
API Mfg. Phenobarbital Sodium, USP Grade P, C-IV:, Re test Date:
Stopper Used 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper Flip Off Seals: 13 mm Red Plastic top flip off with Aluminum Seal
Configuration Inverted Stability 25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial		1 Month DOA: Oct. 31, 2019				3 Months DOA: Jan. 10, 2020				6 Months DOA: Apr. 8, 2020			
		DOA: Sep. 27, 2019		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 (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay Phenobarbital Sodium	90.0%-105.0%	98.4	97.6	98.6	99.0	99.0	100.4	99.1	99.7	97.0	96.9	97.7	98.3	97.2	97.6
% Impurity 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%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 2.0%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031-169 to 183				192039-44 to 52				192045-36 to 85			

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

TABLE 17

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

	NPH1980 (Bulk Solution at 100 mg · mL Phenobarbital Sodium) Compounding at 2-8° Fill Volume 1.0 mL		
Ingredients	mg/mL (after reconstitution)	mg/vial	Batch Quantity (100 mL)
Phenobarbital Sodium	20	100	10.113 g
WFI/DI Water	qs	qs	Qs to 100 mL or 103.3 g

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

Representative chromatograms and/or corresponding calculations are shown in FIGS. **2A-2H**, **3A-3L**, **4A-4L**, and Tables 2 and 3.

The results for further extended stability studies are presented below in which commercially available phenobarbital sodium, USP Grade P was dissolved in water to produce an aqueous solution having a pH of between 9.2 and 10.2, and in which the aqueous solution was then filled into lyophilization vials in an amount of between 65 mg per vial and 200 mg per vial at a maximum concentration of phenobarbital of 100 mg/ml. Lyophilization was performed as in Table 15 noted above. Stability studies were then performed at standard conditions (RT: 25° C., 60% relative humidity) and accelerated conditions (ACC: 40° C., 75% relative humidity) for a period of up to 37 months.

After the storage conditions indicated in the tables below, the lyophilized product was then dissolved in water (or saline or dextrose) and subjected to analysis for degradation products of phenobarbital. Specifically, the inventors investigated the levels of degradation by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Remarkably, and as can be seen from the data below, the lyophilized amorphous phenobarbital had a storage stability at 25° C. and 60% relative humidity for up to and beyond three years and did readily dissolve upon reconstitution.

Table 18 depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

TABLE 18

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

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

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

Table 19 depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

TABLE 19

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

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

TABLE 19-continued

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

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

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

Table 20 depicts exemplary results for 100 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

TABLE 20

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

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

TABLE 20-continued

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

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

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

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

Table 21 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

TABLE 21

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

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

TABLE 21-continued

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

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

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

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

Table 22 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

TABLE 22

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

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

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

Table 22 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 22

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

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

TABLE 22-continued

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

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

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

Table 23 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%). In contrast to Table 22, this formulation was filled into the vial using a 9% saline solution. The final concentration of the saline after reconstitution in 10 mL of water for injection will be 0.9%.

TABLE 23

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

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

TABLE 23-continued

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

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

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

To further investigate if the nature of the reconstitution solution would have an adverse effect on stability after reconstitution, the inventors used 65 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose to a final concentration of 1 mg/ml. In an additional set of experiments, the inventors used 130 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose or water to a final concentration of 20 mg/ml. The so reconstituted solutions were then kept under refrigeration (2-8° C.) or at standard conditions (25° C.) for the indicated times in the tables below. The levels of degradation were determined by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Once more, under all tested conditions, the stability of the so reconstituted compositions was unexpectedly high.

Table 24 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 24

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

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

TABLE 24-continued

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

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

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

Table 25 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 25

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

Admixture study of Phenobarbital Sodium for Injection
USP, 65 mg/vial (NPH2020) (1 mg/mL) dilution in 0.9% Saline)

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

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

Table 26 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 26

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

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

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

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

Table 27 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 27

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

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

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

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

Table 28 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with water to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 28

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

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

TABLE 28-continued

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

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

CCS: Clear colourless solution;

ND: Not detected;

BQL: Below Quantitation limit;

NP: Not performed;

2EPMM: 2-ethylphenylmalonamide monohydrate;

PBG: Phenylbutyrylguanidine;

PEAU: Phenylethylacetylurea

In further experiments, the inventors investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents. To that end, the inventors tested isopropanol, tert-butanol, ethanol, and acetonitrile as co-solvents. Most typically, the co-solvent(s) will be present in an amount of at least 1.0%, or at least 1.5%, or at least 2.0%, or at least 2.5%, or at least 3.0%, or at least 3.5%, or at least 4.0%, or at least 4.5%, or at least 5.0%, or at least 5.5%, or at least 6.0%, or at least 7.0%, or at least 8.0%, or at least 9.0%, or at least 10%, or at least 25%, or at least 50%, or at least 75%. Therefore, suitable quantities of co-solvent(s) include those between 1.0 and 3.0%, or between 2.5% and 5.0%, or between 3.0% and 7.5%, or between 5.0% and 10%, or between 10% and 25%, or between 25% and 50%, or between 50% and 75%, and even higher. For example, and as shown in more detail below, the concentration of the organic co-solvent was as high as 90%. Lyophilization conditions and results are shown below. Tables 29A and 29B depict formulation details used in the lyophilization and stability experiments. Two formulations were prepared for each strength (65 mg and 130 mg), one with 5% Isopropanol and the other with 5% Tertiary Butanol, and other co-solvents (here acetonitrile and ethanol) were also evaluated. The organic solvent was added after the Phenobarbital Sodium was dissolved in water, mixed well and adjusted to final volume with water. Later the bulk solution is filled in vials and lyophilized using the Lyo cycle parameters shown in Table 30. After the Lyo cycle was completed, the finished product was analyzed for assay, related substances, pH, moisture content and residual solvents.

TABLE 29A

Formulations with t-butanol and isopropanol as organic co-solvent

Ingredients	Bulk Solution	CAS Number	Concentration in mL	Total volume (50 mL)
Phenobarbital Sodium, USP C-IV	65 mg/mL	NA	65.73 mg (~65 mg Phenobarbital Sodium after LOD correction)	3.287 g
	130 mg/mL		131.469 mg (~130 mg Phenobarbital sodium after LOD correction)	6.573 g
Tertiary Butanol	5%	75-65-0	(0.05 ml or 0.039 g)	2.5 ml or 1.95 g
Isopropanol		67-63-0	(0.05 ml or 0.0393 g)	2.5 ml or 1.963 g
DI Water/Water for Injection	N/A		Q.S. to 1 mL	Q.S. to 50 mL

TABLE 29B

Formulations with ethanol and acetonitrile as organic co-solvent

Ingredients	Bulk Solution Formulation prepared at 25° C.	Total Volume (100 mL Batch Size) NPH22035	NPH22034
Phenobarbital Sodium	130 mg/mL	13.38 g	13.38 g
Ethanol	Qs	—	Qs to total volume 100 mL
Acetonitrile	Qs	Qs to total volume 100 mL	—
Water for Injection/ DI water	10%	10 ml	10 ml

TABLE 30

Lyophilization protocol

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

TABLE 30-continued

Lyophilization protocol

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

Table 31 depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% tert-butanol) stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

TABLE 31

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

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

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

Table 32 depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% isopropanol) stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05).

TABLE 32

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

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

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

Table 33 depicts initial results for 65 mg and 130 mg per vial lyophilized phenobarbital sodium from respective bulk solutions containing ethanol or acetonitrile as co-solvent (to obtain 65 mg/vial, 0.5 mL of the bulk solution was filled in the vials and for 130 mg/vial strength, 1 ml of the bulk solution was filled in the vials prior to lyophilization). For all test products, 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Notably, unspecified degradation products and total degradation products also remained undetectable or below quantitation limit (0.05%).

TABLE 33

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

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

TABLE 33-continued

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

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

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

Notably, the results indicated that the above formulations were also storage stable over at least three months as evidenced by all known impurities below quantitation limit as shown in Tables 31 and 32. However, an unknown impurity was observed above LOQ level. Interestingly, the residual solvents tertiary butanol and isopropanol were not completely removed after the first cycle of secondary drying. Tertiary butanol and isopropanol were observed above 0.5% in the 65 mg and 130 mg strength products. The same vials were then subjected to additional secondary drying at 25° C. for 30 min and 50° C. for 120 min, and the samples were analyzed for residual solvent after the second cycle of secondary drying.

After the additional secondary drying steps, residual tert-butanol and isopropanol were observed at lower quantities, respectively. As can be readily seen, the organic solvents could be reduced in quantities, but were not completely removed, possibly suggesting that the tested organic solvents could form a bond in the crystal lattice of phenobarbital. However, further process modifications may possibly result in additional reduction of residual co-solvent, requiring extensive experimentation. Similar formulations were prepared in organic solvents ethanol and acetonitrile. Here as well, the residual solvent ethanol was not completely removed, but further process modifications may possibly result in additional reduction of residual co-solvent, requiring extensive experimentation.

Organic solvents such as isopropanol, tertiary butanol, ethanol and acetonitrile were investigated as co-solvents during the lyophilization. Two co solvents tertiary butanol and Isopropanol were used as co-solvents at 5%. The 3M stability data for the formulation with IPA and tert-butanol indicates that although no known degradation products were observed above quantitation limit, the residual solvents could not be removed completely after lyophilization. When ethanol was used as a co solvent similar results were observed. In view of the fact that organic solvents are toxic to all age groups, and in particular to neonates and because residual solvents are typically trapped in the crystal lattice of the Phenobarbital, the lyophilized product with only water as solvent is preferred over formulations containing any organic co solvents.

X-Ray Powder Diffraction. With reference to FIGS. **5**A-**5**D, XRPD was performed using the Rigaku Smart-Lab X-ray diffraction system configured for reflection Bragg-Brentano geometry using a line source X-ray beam. The X-ray source is a Cu Long Fine Focus tube that was operated at 40 kV and 44 mA. That source provides an incident beam profile at the sample that changes from a narrow line at high angles to a broad rectangle at low angles. Beam conditioning slits were used on the line X-ray source to ensure that the maximum beam size is less than 10 mm both along the line and normal to the line. The Bragg-Brentano geometry is a para-focusing geometry controlled by passive divergence and receiving slits with the sample itself acting as the focusing component for the optics. The inherent resolution of Bragg-Brentano geometry is governed in part by the diffractometer radius and the width of the receiving slit used. Typically, the Rigaku Smart-Lab is operated to give peak widths of 0.1° 2θ or less. The axial divergence of the X-ray beam is controlled by 5.0-degree Soller slits in both the incident and diffracted beam paths. The samples were placed in a low-background, silicon holder using light manual pressure to keep the sample surfaces flat and level with the reference surface of the holder. The samples were analyzed from 2 to 40° 2θ using a continuous scan of 6° 2θ per minute with an effective step size of 0.02° 2θ.

The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such

as") provided with respect to certain embodiments herein is intended merely to better illuminate the full scope of the present disclosure and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claimed invention.

It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the full scope of the concepts disclosed herein. The disclosed subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C . . . and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

What is claimed is:

1. A storage stable pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized, and

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

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

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

4. The pharmaceutical product of claim **1**, wherein the composition has the property that when the composition is stored at 40° C. for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

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

6. The pharmaceutical product of claim **1**, wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).

7. A pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized,

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

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

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

9. The pharmaceutical product of claim **7**, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

10. The pharmaceutical product of claim **7**, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

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

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

13. The pharmaceutical product of claim **12**, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

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

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

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

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

18. The pharmaceutical product of claim **8**, wherein the composition has the property that when the composition is stored at room temperature for **6** months and then reconstituted for injection with 10 mL of an aqueous solution to form

a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

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

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

* * * * *

Bibliographic Data

Application No: 18/100,804

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☑ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /CARLOS A AZPURU/ Examiner's Signature | Initials

Title: Lyophilized Compositions of Phenobarbital Sodium Salt

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
01/24/2023	424	1617	
RULE			

APPLICANTS

Nivagen Pharmaceuticals, Inc.,

INVENTORS

Bala Tripura Sundari Chodavarapu, Davis, CA, UNITED STATES

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Jay Shukla, Sacramento, CA, UNITED STATES

Anand Shukla, Denver, CO, UNITED STATES

Dasaradhi Lakkaraju, Sacramento, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 17854914 06/30/2022

17854914 is a CIP of 17025881 09/18/2020 PAT 11406598

17025881 has PRO of 62903511 09/20/2019

FOREIGN APPLICATIONS

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02/14/2023

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STATE OR COUNTRY

UNITED STATES

ADDRESS

FILING FEE RECEIVED

$2,400

Electronic Acknowledgement Receipt	
EFS ID:	47418476
Application Number:	18100804
International Application Number:	
Confirmation Number:	9426
Title of Invention:	LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	104078.0001US3
Receipt Date:	24-JAN-2023
Filing Date:	
Time Stamp:	15:10:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2400
RAM confirmation Number	E20231NF11240858
Deposit Account	601823
Authorized User	Danielle Moroz
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ADS.pdf	2277863 6453066dd4944e55000f67dd4cfe2e05c7e2e1095	no	10
Warnings:					
Information:					
2	Track One Request	Track1_Req.pdf	120910 8fe7d4359608bdf99ff7abce2585d92eb339d24bd	no	2
Warnings:					
Information:					
3		APP-FILED_2023-01-11_REV002.pdf	4569206 a6031c9f7a879499f2e9d174a1917e1d6ea602af	yes	97

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	54
Claims	55	57
Abstract	58	58
Drawings-other than black and white line drawings	59	97

Warnings:					
Information:					
4	Oath or Declaration filed	Declaration_Anand_Shukla_Signed.pdf	918348 c217b012984bc6a79e3043e7aaf889cefa3fc179	no	1
Warnings:					
Information:					

5	Oath or Declaration filed	Declaration_Chodavarapu_Signed.pdf	939567 cad9906878198c2cf2a827d3a4721d915d6fc158	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	Declaration_Jay_Shukla_Signed.pdf	918558 9a1678ac210d93109cd6abf82458d45438aaca685	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	Declaration_Lakkaraju_Signed.pdf	927594 73fb762ef11c490c49c2b4ce319d07af07ac2105	no	1
Warnings:					
Information:					
8	Oath or Declaration filed	Declaration_Mangali_Signed.pdf	925855 1d88dced4fb109al2b7e911d821324eaa8c5d3a	no	1
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	50929 b2d38aaaee22a98dc134c8e777818a25e052a66b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	11648830		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bala	Tripura Sundari	Chodavarapu	

Residence Information (Select One) • US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
Davis	CA	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	State/Province	Postal Code	Country i
Sacramento	CA	95827	US

Inventor 2 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Thirupathi		Mangali	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
Sacramento	CA	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	State/Province	Postal Code	Country i
Sacramento	CA	95827	US

Inventor 3 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jay		Shukla	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

City	Sacramento	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anand		Shukla	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Denver	State/Province	CO	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dasaradhi		Lakkaraju	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Sacramento	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Customer Number	149344		
Email Address	patents@umbergzipser.com	Add Email	Remove Email

Application Information:

Title of the Invention	Lyophilized Compositions of Phenobarbital Sodium Salt		
Attorney Docket Number	104078.0001US3	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	39	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	• Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	149344		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	17854914	2022-06-30

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17854914	Continuation in part of	17025881	2020-09-18	11406598	2022-08-09

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17025881	Claims benefit of provisional	62903511	2019-09-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

• Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Nivagen Pharmaceuticals, Inc.		
Mailing Address Information For Applicant:			
Address 1	3050 Fite Circle, Suite 100		
Address 2			
City	Sacramento	**State/Province**	CA
Country	US	Postal Code	95827
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Nivagen Pharmaceuticals, Inc.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	3050 Fite Circle, Suite 100		
Address 2			
City	Sacramento	**State/Province**	CA
Country	US	Postal Code	95827
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Martin Fessenmaier/			Date (YYYY-MM-DD)	2023-01-24
First Name	Martin	Last Name	Fessenmaier	Registration Number	46697

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US3
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Bala Tripura Sundari Chodavarapu	Nonprovisional Application Number (if known):	
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Martin Fessenmaier/	Date January 24, 2023
Name (Print/Typed) Martin Fessenmaier	Practitioner Registration Number 46697

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT

Related Applications

[0001] This application is a continuation application of our co-pending US application with the serial number 17/854,914, filed 6/30/2022, which is a continuation-in-part application of our US application with the serial number 17/025,881, filed 9/18/2020, now US patent 11,406,598, which claims the benefit of United States Provisional Patent Application No. 62/903,511, filed on September 20, 2019, which is incorporated by reference in its entirety.

Field of the Invention

[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.

Background of the Invention

[0003] The background description includes information that may be useful in understanding the present disclosure. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic. Phenobarbital Sodium is typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals

dissolved in an aqueous solvent. For example, WO 2017/085687 to Parker et al. discloses a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol.

[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.

[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.

[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 or130 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.

[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.

Summary

[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.

[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.

[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.).

[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.

[0014] In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (*e.g.*, Water for Injection) is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[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).

[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.

[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).

[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.

[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.

[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 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.

[0021] In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[0022] For adjusting the pH of the Phenobarbital Sodium solution, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution 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).

[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.

[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.

[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.

[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.

[0027] Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium.

[0028] Various objects, features, aspects, and advantages will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawings.

Brief Description of Drawings

[0029] **Fig. 1A** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -50°C, as indicated.

[0030] **Fig. 1B** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -45.5°C as indicated.

[0031] **Fig. 1C** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -40.0°C as indicated.

[0032] **Fig. 1D** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -39.6°C as indicated.

[0033] **Fig. 1E** is a **polarized** light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -39.2°C as indicated.

[0034] **Fig. 1F is** a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -38.8°C as indicated.

[0035] **Fig. 2A** is a chromatogram from an injection of a "blank solution" for assay by high performance liquid chromatography (HPLC) at a detection wavelength of 210 nanometers (nm), as described herein.

[0036] **Fig. 2B** is a chromatogram from an injection of the "Sensitivity solution" of Phenobarbital for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0037] **Fig 2C** is a chromatogram from an injection of a "related substance" (RS) working standard at 0.2% impurity level) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0038] **Fig. 2D** is a chromatogram from an injection of 2-ethyl-2-phenylmalonamide (2EPMM) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0039] **Fig. 2E** is a chromatogram from an injection of alpha-phenylbutyrylguanidine (PBG) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0040] **Fig. 2F** is a chromatogram from an injection of phenylethylacetylurea (PEAU) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0041] **Fig. 2G** is a chromatogram from an injection of a "blank solution" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0042] **Fig. 2H** is a chromatogram from an injection of an "assay working standard" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0043] **Fig. 3A** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0044] **Fig. 3B** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0045] **Fig. 3C** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0046] **Fig. 3D** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0047] **Fig. 3E** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0048] **Fig. 3F** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0049] **Fig. 3G** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0050] **Fig. 3H** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0051] **Fig. 3I** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0052] **Fig. 3J** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0053] **Fig. 3K** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0054] **Fig. 3L** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability

conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0055] **Fig. 4A** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0056] **Fig. 4B** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0057] **Fig. 4C** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0058] **Fig. 4D** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0059] **Fig. 4E** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0060] **Fig. 4F** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0061] **Fig. 4G** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0062] **Fig. 4H** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0063] **Fig. 4I** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0064] **Fig. 4J** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0065] **Fig. 4K** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0066] **Fig. 4L** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0067] **Fig. 5A** is an X-ray powder diffraction (XRPD) pattern of Phenobarbital Sodium Grade P

[0068] **Fig. 5B** is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

[0069] **Fig. 5C** is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

[0070] **Fig. 5D** is a stack plot of the XRPD patterns of **Figs. 5A**, **5B**, and **5C**.

Detailed Description

[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).

[0072] The Phenobarbital Sodium composition as described herein refers to Phenobarbital Sodium having an IUPAC (International Union of Pure and Applied Chemistry) name of sodium 5-ethyl-4,6-dioxo-5-phenyl-1*H*-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$.

[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.

[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 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 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.

[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 (O_2) gas from the water (*e.g.*, Water for Injection), it is also preferred that the water is sparged with nitrogen (N_2) 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.

[0076] The addition of the Phenobarbital Sodium solid to the water (*e.g.*, deionized nitrogen sparged water cooled to 2 to 8°C) may be carried out using any suitable mixing. Preferably, the water (*e.g.*, Water for Injection) is first added to a glass/stainless steel container for nitrogen sparging and cooling, and this prepped water remains in the glass/stainless steel container or a measured amount is transferred to a preferably weighed glass container/stainless steel container and the Phenobarbital Sodium solid is added thereto. For mixing, any suitable mixing may be used. For example, a magnetic stir bar may be added to the glass/stainless steel container. Upon addition of the Phenobarbital Sodium solid to the water, the mixture is stirred.

[0077] An additional consideration for stability of the Phenobarbital Sodium is maintaining a pH between 9.2 and 10.2 in the bulk solution of Phenobarbital Sodium. After dissolution of the Phenobarbital Sodium solid in the water, the pH is adjusted to within this range of 9.2 and 10.2.

Accordingly, the pH of the water solubilized Phenobarbital Sodium is first measured upon dissolution. If the pH is higher than 10.2 or lower than 9.2, the pH is adjusted. For example, if necessary, the pH may be lowered to or between 9.2 and 10.2 using Hydrochloric acid (HCl) and the pH may be increased to or between 9.2 and 10.2 using Sodium Hydroxide (NaOH).

[0078] Following the pH measurement and any adjustment, the Phenobarbital Sodium solution is preferably filtered to remove any foreign particles. For example, the Phenobarbital Sodium solution may be filtered using a 0.2 μm (or 0.22 μm) membrane filter. For example, the membrane filter may be polyvinylidene difluoride (PVDF) or any other compatible filter membranes such as Polyethersulfone (PES) filter.

[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.

[0080] In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum.

[0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium.

[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.

[0083] In one embodiment, the water is Water for Injection.

[0084] In another embodiment the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.

[0085] In another embodiment, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.

[0086] In another embodiment, the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[0087] In another embodiment, the adjusting includes measuring the pH of the Phenobarbital Sodium solution, and if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

[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).

[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).

[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).

[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).

[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.

[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.

[0094] In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing.

[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.

[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.

[0097] In another embodiment, the individual suffers from epilepsy.

[0098] In another embodiment, the individual is a newborn suffering from neonatal epilepsy.

[0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

[00100] In another embodiment, the administering includes intramuscular injection or intravenous injection.

[00101] 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.

[00102] 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**.

[00103] **Table 1**

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**

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

[00104] 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**).

[00105] Table 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder												
Product Name		Phenobarbital Sodium for Injection USP, 65 mg/mL (Marketed product)					Phenobarbital Sodium for Injection USP, 65 mg/Vial (Nivagen formulation- NPH1907)					
Formulation Type		Liquid					Lyophilized powder					
	Stability Data											
Test	**Initial**	**3 Months**		**6 Months**			**Initial**	**3 Months**		**6 Months**		**15 Months**
		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**	**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											

Notably, the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration.

[00106] 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					
Test	**Stability Data**											
	Initial	**3 Months**		**6 Months**			**Initial**	**3 Months**		**6 Months**		**15 Months**
		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**	**ACC 40°C, 75% RH**	**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**	**RT** 25°C, 60% RH**
Description	CCVS	CCVS	CCVS	CCVS	CCVS		WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA		CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$		$	$	$	$	$	$
pH*	9.5	9.9	9.9	9.8	9.7		9.8	9.8	9.8	9.8	9.8	10.0
% Assay of Phenobarbital Sodium	100.8	95.5	92.9	95.2	90.9		98.3	100.1	97.9	100.2	99.4	98.3
Related Substances (% Area) 2EPMM	ND	ND	BQL	BQL	BQL		ND	ND	ND	ND	ND	ND
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											

[00107] 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.

[00108] 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.

[00109] 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.

Examples

[00110] Lyophilization Microscopy. Lyophilization microscopy (**Figs. 1A-1F**) was performed using a Leica DM LP microscope equipped with a Linkam FDCS196 stage, TMS93 controller, vacuum pump, LNP unit, and a Spot Insight color camera. A 20x, 040 N.A. objective was used with crossed polarizers and a first order red compensator to view sample. Images were acquired using Spot Advanced software (v.4.5.9).

[00111] 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.

[00112] HPLC Assays. High Performance Liquid Chromatography (HPLC) was used to assay Phenobarbital Sodium standards and sample solutions as disclosed herein (*e.g.*, **Tables 2**, **3**, **Figs. 2A-2H, 3A-3L, and 4A-4L**). Both Ultra High-Performance Liquid Chromatographic system (UHPLC) and High-Performance Liquid Chromatographic system (HPLC) (ThermoFisher/Waters) were used together with Data Acquisition Software (Empower 3), equipped with UV and Photodiode Array Detector (UV and PDA), column thermostat and auto sampler compartments or equivalent HPLC system and software.

[00113] An exemplary HPLC assay protocol is provided in the following:

[00114] Instruments / Apparatus: HPLC with UV detector / PDA Detector, Analytical balance, Sonicator, Volumetric flasks, Beakers, Pipettes.

[00115] Reagents, Solvents, Standards: Phenobarbital Reference Standard, Deionized water / Water for Injection, Potassium Monobasic Phosphate, Acetonitrile.

[00116] Preparation of Mobile Phase Solutions: Potassium phosphate monobasic (7 mM) and Acetonitrile (70:30) pH 4.5-6.5; Diluent: Mobile phase as a diluent.

[00117] Wash Solvent: Water: Acetonitrile (70:30)

[00118] CHROMATOGRAPHIC CONDITIONS: The liquid chromatography equipped with a

Parameters	Conditions
Column	L7 packaging column , 150 X 4.6 mm, Particle Size : 5µm or equivalent
Flow rate	0.9- 1.2 mL /min.
Detection Wavelength	254± 2 nm for assay and 210± 2 nm for Related Substances
Injection volume	10 µL
Run time	15 Minutes
Column Oven Temperature	30°C
Sampler Cooler Temperature	25°C
Retention Time	About 5 minutes for Phenobarbital
Pump Mode	Isocratic

UV and PDA detector, an injector and a data processor is operated as follows:

[00119] Phenobarbital Assay Standard Solution: 0.2 mg/mL to 0.8 mg/mL in diluent; Phenobarbital Related Substances Standard Solution: 0.26 µg/mL to 15.6 µg/mL in diluent; Phenobarbital Related Substances resolution standard solution: 0.475 mg/mL Phenobarbital and about 1 µg/mL for related substances (2-Ethyl-2-Phenyl malonamide, monohydrate (2EPMM), Phenylbutyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) in diluent; Phenobarbital Sodium Sample Solution for Assay: 0.26 mg/mL to 0.78 mg/mL in diluent

[00120] Phenobarbital Sodium related Substances sample solution: 0.52 mg/mL of Phenobarbital Sodium and related substances 2-Ethyl-2-Phenylmalonamide, monohydrate (2EPMM), Phenyl butyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) and any unspecified degradation products at 0.26 µg/mL to 13. 2 µg/mL

[00121] SYSTEM SUITABILITY REQUIREMENTS: The relative standard deviation of Phenobarbital peak from Six replication injections of related substances standard should not be more than 6.0%. The related standard deviation of Phenobarbital peak from five replicate injections in assay standard solution should not be more than 2.0%. Tailing factor for the Phenobarbital is not more than 2.0. USP Plate count for the Phenobarbital is not less than 2500. The S/N Ratio of the Sensitivity Standard Solution is NLT 10 for related substance test. The resolution between Phenobarbital peak and nearest impurity peak is NLT 1.5

[00122] 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.

[00123] Table 6. Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

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

Ingredients	NPH2031 A (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°C		NPH2031 A (Bulk Solution at 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	20	200	20	200
Sodium Chloride	NA	NA	9	90
WFI/DI Water	qs	qs	qs	qs

[00124] 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**).

[00125] Table 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	Spec.	Initial DOA: 06/05/20	Reconstituted Solution Stability after 20 hrs DOA: 06/06/2020	
			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
Note Book Reference		192045-165 to 189	192045-163-185	
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				

[00126] Table 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)				
Test	Specification	Initial	Reconstituted Solution Stability after 20 hrs	
			2-8°C	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5 %	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
WLP: White Lyophilized Powder; CCS. Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00127] Table 9

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

[00128] 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**.

[00129] Table 10

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch=NPH2020 Fill Volume: 1.05 mL	Date Manufactured:01/20/2020
Vial Make: 2 mL Clear Glass Vial; Stopper: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal. API: Phenobarbital Sodium, USP Grade P			
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 02/18/20	1 Month DOA: 03/23/2020		3 Months DOA:05/20/20		6 Months DOA: 09/04/2020	
			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	9.6	9.6
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.6	101.6	101.5	101.5	100.5	100.0	101.2
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEA#	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%	0.7	0.9	1.3	1.4	1.5	1.6	2.1
Note Book Reference		192039-130 to 158	192045- 23 to 45		192045-135 to 151		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, monoglycinate; PBG: α-Phenylbenzylglycine; PEAU: Phenylethylacetylurea ;

[00130] Table 11

Product Name	**Phenobarbital Sodium for Injection USP,** 130 mg/vial	**Batch#**NPH2021 Fill Volume: 1.05 mL	**Date Manufactured**:01/20/2020
Vial Make	2 mL Clear Glass Vial		**Date Initiated**:02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P. **Re test Date:** 11/16/2023		
Stopper Used	13 mm Grey Rubber stopper	**Flip Off Seals**:13mm Plastic with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**		**24 Months**
			DOA: 03/23/2020		**DOA:05/20/20**		**DOA:09/04/20**		**DOA: 18-Mar-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0 %	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099-157,158,167,170

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

[00131] Table 12

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial	**Batch#**NPH203iA Fill Volume: 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper	**Flip Off Seals**:20 mm Red Plastic top flip off with Aluminum Seal , Lot#224203	
Configuration	Inverted **Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)	

Test	Spec.	Initial DOA: 06/05/20	3 Months DOA: 09/04/2020	
			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	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5 %	BQL	0.06	0.05
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.1
Note Book Reference		192045-163 to 189	192651- 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-Phenylbutyryliguamdine; PEAU: Phenylethylacetylurea

[00132] Table 13

Product Name	**Phenobarbital Sodium for Injection USP,** 200 mg/vial (Phenobarbital Sodium and 9% Saline vial)	**Batch**#NPH2031B Fill Volume. 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium. USP Grade P. C-IV **Re test Date**: 07/20/2024		
Stopper Used	20 mm Lyophilization Rubber stopper		**Flip Off Seals**: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months		6 Months		12 months
			DOA: 09/04/2020		DOA: 12/11/20		DOA: 11-Apr-22
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137

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

[00133] Data for Osmolality, Particulate matter and assay for Sodium Chloride is disclosed in **Table 14**.

[00134] 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>		Assay of Sodium Chloride (titrimetric; Ref USP monograph for Sodium Chloride Injection
		≥10 µM Specification: (NMT 6000 particles/vial)	≥25 µM Specification: (NMT 600 particles/vial	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

[00135] Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in **Table 15**.

[00136] Table 15. Lyophilization Cycle parameters.

Section	Phase	Lyophilization Cycle 1*				Lyophilization Cycle 2**			
		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)
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)**

[00137] Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in **Table 16**.

[00138] Table 16

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**/PH1980 Fill Volume: 1.0 mL	**Date Manufactured**: 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		**Date Initiated**: 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P_C-IV's; **Re test Date:**		
Stopper Used	13 mm Grey *Bromobutyl* 2 leg *Lyophilization* Rubber stopper	**Flip Off Seals**: 13mm Red Plastic top flip off with *Aluminum* Seal	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec	Initial DOA:09/27/2019		1 Month DOA:10/31/2019				3 Months DOA:01/10/2020				6 Months DOA:04/08/2020			
		UT	T	RT		ACC		RT		ACC		RT		ACC	
				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 (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.8	9.8	9.9
% Assay of Phenobarbital	90.0%-105.0 %	98.4	97.8	98.8	99.0	98.0	100.4	99.1	98.2	97.9	98.9	97.7	98.3	97.2	97.6
% Impurity 2EPAM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
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%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 3.0 %	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	0.9	1.1	1.1	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031-169 to 183				192039-44 to 52				192563-45 to 85			

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

[00139] Table 17. Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

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

Ingredients	NPH1980 (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°		
	Fill Volume 1.0 mL		
	mg/mL (after reconstitution)	mg/vial	Batch Quantity (100 mL)
Phenobarbital Sodium	20	100	10.113 g
WFI/DI Water	qs	qs	Qs to 100 mL or 103.3 g

[00140] Representative chromatograms and/or corresponding calculations are shown in **Figs. 2A-2H, 3A-3L, 4A-4L,** and **Tables 2** and **3**.

[00141] The results for further extended stability studies are presented below in which commercially available phenobarbital sodium, USP Grade P was dissolved in water to produce an aqueous solution having a pH of between 9.2 and 10.2, and in which the aqueous solution was then filled into lyophilization vials in an amount of between 65 mg per vial and 200 mg per vial at a maximum concentration of phenobarbital of 100 mg/ml. Lyophilization was performed as in Table 15 noted above. Stability studies were then performed at standard conditions (RT: 25 °C, 60% relative humidity) and accelerated conditions (ACC: 40 °C, 75% relative humidity) for a period of up to 37 months.

[00142] After the storage conditions indicated in the tables below, the lyophilized product was then dissolved in water (or saline or dextrose) and subjected to analysis for degradation products of phenobarbital. Specifically, the inventors investigated the levels of degradation by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Remarkably, and as can be seen from the data below, the lyophilized amorphous phenobarbital had a storage stability at 25 °C and 60% relative humidity for up to and beyond three years and did readily dissolve upon reconstitution.

[00143] **Table 18** depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

[00144] **Table 18 (65 mg/vial, up to 24 months)**

Product Name	**Phenobarbital Sodium for Injection USP, 65 mg/vial**	**Batch=**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured:**01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vials		**Date Initiated:**02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C /60 % RH (RT) & 40°C /75 % RH (ACC)

Test	Spec.	Initial DOA: 02/19/20	1 Month DOA: 03/23/2020		3 Months DOA:05/20/20		6 Months DOA: 09/04/2020		24 months DOA: 15-MAR-2021
			RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6	9.7
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.6	101.6	101.5	101.3	100.5	100.9	101.2	101.2
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.9	1.3	1.4	1.5	1.6	2.1	1.8
Note Book Reference		592009-150 to 158	192045-23 to 45		192045-135 to 171		192031-84 to 122		[illegible]

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-Phenylbutyrolactone; PEAU: Phenylethylacetylurea.

[00145] **Table 19** depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00146] **Table 19 (65 mg/vial, up to 37 months)**

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/Vial	Batch#PH1907	Date Manufactured: 02/21/2019
Vial Make	2 mL Flint Clear Blow Back Vial		Date Initiated: 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	Flip Off Seal: 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	Stability	25°C ± 2°C, 60 % RH ± 5% (RT) & 40°C ± 2°C, 75 % RH ± 5% (ACC)

Test	Spec.	Initial DOA: 02/25/2019	1 Month DOA: 03/28/2019		3 Months DOA: 05/24/2019		6 Months DOA: 08/28/2019		12 Months DOA: 06/12/2020	37 Months
			RT	ACC	RT	ACC	RT	ACC	*RT	**RT
Description	White to almost white lyophilized powder	~	~	~	~	~	~	~	~	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of reconstituted solution	8.5-9.5	9.3	9.0	9.0	9.0	9.0	9.0	9.0	9.0	
% Assay Phenobarbital Sodium	90.0%-110.0%	99.1	98.4	98.2	98.3	98.4	98.6	98.3	98.6	
Related Substances: 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	<LOQ	
Total degradation products	NMT 0.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	<LOQ	
Water Content by Karl Fischer	NMT 3.0%	0.9	1.1	1.7	1.6	1.5	2.2	1.8	2.6	
Note Book Reference		2000/9-11,88,89,19	1928/49-52,120,126-127		1938/25-29,30,31,36		1970/01-03,111,115,117,18		2085/12-16,21	

BQL: Below of Analysis
WFI: Water Lyophilized Powder, U.S.P. Clear Solution Solution, Colorless Non-Viscous Solution.
ND: Not Detected, NMT: Not More Than, BQL: Below Quantitation Limit (0.05%).
2EPMM: 2-Ethyl-2-Phenylmalonamide, PBG: 2-Phenylglycinamide, PEAU: Phenylacetylurea.
*The samples were stored at 40°C ± 2°C, 75% (RH) ± 5%. ** The samples were stored from 30°C ± 2°C/ 65% (RH) ± 5% and stored at 2°C ± 2°C, 60%(RH) ± 5% as 15 months time point.

[00147] **Table 20** depicts exemplary results for 100 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00148] **Table 20 (100 mg/vial, up to 30 months)**

Product Name	Phenobarbital Sodium for Injection USP, 130 mg/vial	Batch#:9921500 Fill Volume: 1.0 mL	Date Manufactured: 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		Date Initiated: 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.		
Stopper Used	13 mm Gray Bromobutyl 2 leg Lyophilization Rubber stopper	Flip Off Seals: 13mm Red Plastic top flip off with Aluminum Seal Lot# NA	
Configuration	Intercid	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial: DOA:09/27/2019		6 Month: DOA:10/31/2019				3 Months: DOA:01/10/2020				6 Months: DOA:04/08/2020				36 Months: DOA: 15-MAR-2022	
		UT	T	RT		ACC		RT		ACC		RT		ACC		RT	
				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	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9	9.6	9.6
% Assay of Phenobarbital	90.0%-105.0%	98.4	97.6	98.6	99.0	98.9	100.4	99.1	98.7	97.9	96.9	97.7	98.3	97.2	97.6	99.2	100.9
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 1.5 %	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.5	1.4	1.6	1.2	1.5	2.9	2.3	1.8
Note Book Reference		192031-93 to 101		192031-369 to 188				192039-44 to 52				192045-46 to 35				192039-157,159,161,171 9157,159,165, 170	

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

[00149] **Table 21** depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00150] **Table 21 (130 mg/vial, up to 37 months)**

Product Name	Phenobarbital Sodium for Injection USP, 130 mg/vial	Batch=NPH1912	Date Manufactured: 02/23/2019
Vial Make	2 ml. Fiolax Clear Blow Back Vial		Date Initiated: 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	Flip Off Seals: 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	Stability	25°C ± 2°C, 60 % RH ± 5% (RT) & 40°C ± 2°C, 75 % RH ± 5% (ACC)

Test	Spec	Initial DOA: 02/25/2019	1 Month DOA: 03/25/2019		3 Months DOA: 05/24/2019		6 Months DOA: 08/28/2019		15 Months DOA: 06/12/2020	37 Months DOA: 18-MAR-2022
			RT	ACC	RT	ACC	RT	ACC	RT	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/ml)	9.2-10.2	9.5	10.0	9.9	9.8	9.8	9.5	9.5	10.0	9.8
% Assay: Phenobarbital Sodium	90.0%-105.0 %	92.5	97.1	98.3	100.1	97.9	96.9	98.4	98.3	99.2
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	0.03	BQL	BQL
Total Degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	0.03	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.6	1.1	1.2	1.3	1.5	2.0	2.4	2.4	1.5
Note Book Reference		192019-41,44,45,47	192019-122,125,126,126		192025-24 30,31,34		192031-8,12,14,16,17,18		192051-2 to 11	192069-157,159,167, 170

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

[00151] **Table 22** depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

[00152] **Table 22 (130 mg/vial, up to 24 months)**

Product Name	**Phenobarbital Sodium for Injection USP**, 130 mg/vial	**Batch#**NPH2021 Fill Volume: 1.05 mL	**Date Manufactured**:01/20/2020
Vial Make	2 mL Piolax Clear Blow Back Vial		**Date Initiated**:02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals**:13mm Red Plastic top flip off with Aluminum Seal	
Configuration	inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 02/18/20	1 Month DOA: 03/23/2020		3 Months DOA:05/20/20		6 Months DOA:09/04/20		24 Months DOA: 18-Mar-2022
			RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0 %	100.5	99.7	99.3	100.0	99.6	99.1	98.3	99.5
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.6	1.3	1.4
Note Book Reference		192059-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 123		192099-157,159,167,170

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

[00153] **Table 22** depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00154] **Table 22 (200 mg/vial, up to 22 months)**

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial	**Batch#**NPH2031A Fill Volume: 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV:		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper	**Flip Off Seals**: 20 mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months DOA: 09/04/2020		6 months DOA: 12/11/2020		22 months DOA: 11-Apr-2022
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7	9.7	9.7	9.5
% Assay Phenobarbital Sodium	90.0 -105.0	100.1	98.1	101.0	100.8	102.5	98.2
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.05	(BQL)
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3	1.2	1.6	1.5
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137

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

[00155] **Table 23** depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%). In contrast to Table 22, this formulation was filled into the vial using a 9% saline solution. The final concentration of the saline after reconstitution in 10 mL of water for injection will be 0.9%.

[00156] **Table 23 (200 mg/vial, up to 12 months)**

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial (Phenobarbital Sodium and 9% Saline vial)	**Batch#**NPH203IB Fill Volume: 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper	**Flip Off Seals**:20 mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months		6 Months		12 months
			DOA: 09/04/2020		DOA: 12/11/20		DOA: 11-Apr-22
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 188	192051- 84 to 122		192067-78 to 88		192034-137

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

[00157] To further investigate if the nature of the reconstitution solution would have an adverse effect on stability after reconstitution, the inventors used 65 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose to a final concentration of 1 mg/ml. In an additional set of experiments, the inventors used 130 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose or water to a final concentration of 20 mg/ml. The so reconstituted solutions were then kept under refrigeration (2-8 °C) or at standard conditions (25 °C) for the indicated times in the tables below. The levels of degradation were determined by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Once more, under all tested conditions, the stability of the so reconstituted compositions was unexpectedly high.

[00158] **Table 24** depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below

quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00159] Table 24 (65 mg/vial, reconstituted to 1 mg/ml in 5% dextrose, up to 24 hrs)

Admixture Study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2020) (1 mg/mL dilution in 5% Dextrose)														
Specification	Tests/Time	Initial	1 hr		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs	
			2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Complies	Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1mg/mL dilution)	8.8	8.8	8.8	8.8	8.8	8.8	8.7	8.8	8.7	8.7	8.7	8.7	8.5
Assay 90% 105%	Assay of Phenobarbital Sodium	95.4	95.7	95.6	95.9	96.4	95.9	97.1	95.6	95.9	94.6	97.1	95.1	95.1
2EPMM NMT0.2%	Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT0.2%	PEAU	ND	ND	BQL	BQL	BQL	ND	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @ RRT 0.29	ND	ND	BDL	ND	BDL	ND	BDL	ND	0.02	BDL	0.02	BDL	0.03
	Any unspecified degradation product @ RRT 0.37	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.03	0.02	0.05
Osmolality To be reported	Osmolality (mOsmol/Kg)	254	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	255	253
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.08
CCS: Clear colourless solution; ND: Not detected; BDL: Below detection limit; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyryldiguanadine; PEAU: Phenylethylacetylurea														

[00160] Table 25 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00161] Table 25 (65 mg/vial, reconstituted to 1 mg/ml in 0.9% saline, up to 24 hrs)

Specifications	Admixture study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2020) (1 mg/mL dilution in 0.9% Saline)												
	Tests/Time	Initial	1 hr.		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs
			2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Complies	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported.	pH (1mg/mL dilution)	9.0	8.8	8.9	9.0	9.0	8.9	8.9	8.8	8.9	8.7	8.8	8.5	8.4
Assay 90%-105%	Assay of Phenobarbital Sodium	95.8	96	94.3	95.4	93.6	95.5	95.2	95.8	93.9	94.6	96.4	95.2	95.3
2EPMM NMT 0.2%	Related Substances (%Area): 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT 0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT 0.2%	PEAU	BQL	ND	BQL	BQL	BQL	BQL	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @ RRT 0.29	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
	Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.03	0.02	0.03	0.02	0.04	0.02	0.04	0.03	0.05	0.03	0.1
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	0.1
Osmolality To be reported.	Osmolality (mOsmol/Kg)	288	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	286	287
CCS: Clear colorless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbenzoylguanidine; PEAU: Phenylethylacetylurea BQL: Below Quantitation limit (0.05%)														

[00162] **Table 26** depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00163] **Table 26 (130 mg/vial, reconstituted to 20 mg/ml in 0.9% saline, up to 24 hrs)**

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In 0.9%Saline)													
Tests/Time	Initial	30 min		90 min		240 min		6 hrs		9.5 hrs		24 hrs	
		2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.3	9.4	9.4	9.4	9.4	9.4	9.2	9.4	9.3
Assay of Phenobarbital Sodium	104.1	103.6	102.4	103.3	102.7	103.2	102.9	103.4	102.9	99.5	103.3	103.2	101.3
Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	BQL	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	BQL	0.03	0.04	0.03	0.05	0.03	0.07	0.03	0.09	0.03	0.13	0.04	0.24
Total degradation products	BQL	0.03	0.04	0.03	0.05	0.03	0.07	0.03	0.09	0.03	0.13	0.04	0.24
Osmolality (mOsmol/Kg)	418	NP	NP	NP	NP	NP	NP	NP	NP	420	418	417	419
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea													

[00164] **Table 27** depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00165] **Table 27 (130 mg/vial, reconstituted to 20 mg/ml in 5% saline, up to 24 hrs)**

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In 5% Dextrose)													
Tests/Time	Initial	30 min		90 min		4 hrs		6 hrs		9.5 hrs		24 hrs	
		2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.4	9.4	9.3	9.3	9.3	9.4	9.3	9.4	9.4
Assay of Phenobarbital Sodium	101	102	100	101.5	102	100.9	101.1	101.7	101.6	101.6	102.1	102.4	102.2
Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.03	0.03	0.04	0.03	0.06	0.03	0.08	0.03	0.11	0.04	0.19
Total degradation products	0.02	0.02	0.03	0.03	0.04	0.03	0.06	0.03	0.08	0.03	0.11	0.04	0.19
Osmolality (mOsmol/Kg)	379	NP	NP	NP	NP	NP	NP	NP	NP	379	386	377	379
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU:Phenylethylacetylurea													

[00166] **Table 28** depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with water to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00167] **Table 28 (130 mg/vial, reconstituted to 20 mg/ml in water, up to 24 hrs)**

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)							
Tests/Time	**Initial**	**2 hrs**		**4 hrs**		**24 hrs**	
		2-8C	**RT**	**2-8C**	**RT**	**2-8C**	**RT**
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	158	NP	NP	NP	NP	159	158
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU:Phenylethylacetylurea							

[00168] In further experiments, the inventors investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents. To that end, the inventors tested isopropanol, tert-butanol, ethanol, and acetonitrile as co-solvents. Most typically, the co-solvent(s) will be present in an amount of at least 1.0%, or at least 1.5%, or at least 2.0%, or at least 2.5%, or at least 3.0%, or at least 3.5%, or at least 4.0%, or at least 4.5%, or at least 5.0%, or at least 5.5%, or at least 6.0%, or at least 7.0%, or at least 8.0%, or at least 9.0%, or at least 10%, or at least 25%, or at least 50%, or at least 75%. Therefore, suitable quantities of co-solvent(s) include those between 1.0 and 3.0%, or between 2.5% and 5.0%, or between 3.0% and 7.5%, or between 5.0% and 10%, or between 10% and 25%, or between 25% and 50%, or between 50% and 75%, and even higher. For example, and as shown in more detail below, the concentration of the organic co-solvent was as high as 90%. Lyophilization conditions and results are shown below. **Tables 29A and 29B** depict formulation details used in the lyophilization and stability experiments. Two formulations were

prepared for each strength (65 mg and 130 mg), one with 5% Isopropanol and the other with 5% Tertiary Butanol, and other co-solvents (here acetonitrile and ethanol) were also evaluated. The organic solvent was added after the Phenobarbital Sodium was dissolved in water, mixed well and adjusted to final volume with water. Later the bulk solution is filled in vials and lyophilized using the Lyo cycle parameters shown in **Table 30**. After the Lyo cycle was completed, the finished product was analyzed for assay, related substances, pH, moisture content and residual solvents.

[00169] **Table 29A** – Formulations with t-butanol and isopropanol as organic co-solvent

Ingredients	Bulk Solution	CAS Number	Concentration in mL	Total volume (50 mL)
Phenobarbital Sodium, USP C-IV	65 mg/mL	NA	65.73 mg (~65 mg Phenobarbital Sodium after LOD correction)	3.287g
	130 mg/mL		131.469mg (~130 mg Phenobarbital sodium after LOD correction)	6.573g
Tertiary Butanol	5%	75-65-0	(0.05 ml or 0.039 g)	2.5 ml or 1.95g
Isopropanol		67-63-0	(0.05 ml or 0.0393 g)	2.5 ml or 1.963 g
DI Water/Water for Injection	N/A		Q.S. to 1 mL	Q.S. to 50 mL

[00170] **Table 29B** – Formulations with ethanol and acetonitrile as organic co-solvent

Ingredients	Bulk Solution Formulation prepared at 25°C	Total Volume (100 mL Batch Size)	
		NPH22035	NPH22034
Phenobarbital Sodium	130 mg/mL	13.38 g	13.38 g
Ethanol	Qs	-	Qs to total volume 100 mL
Acetonitrile	Qs	Qs to total volume 100 mL	-
Water for Injection/ DI water	10%	10 ml	10 ml

[00171] **Table 30** – Lyophilization protocol

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

[00172] **Table 31** depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% tert-butanol) stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00173] **Table 31 (65/130 mg/vial, 5% tert-butanol, up to 3 months)**

Product Name	Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution prepared in 5% Tertiary Butanol					Date Manufactured:02/21/2019 Date Initiated:09/05/2019		
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)					
Test	Spec.	NPH1965 (65 mg/vial)				NPH1967 (130 mg/vial)		
		Initial DOA: 9/07/2019	3 Months DOA: 12/20/2019			Initial DOA: 12/20/2019	3 Months DOA: 12/20/2019	
			RT	ACC			RT	ACC
Description	WLP	WLP	WLP	WLP		WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS		CCS	CCS	CCS
pH (65 mg/mL) pH (100 mg/mL) for 130 mg/vial strength	9.2-10.2	9.7	9.7	9.7		9.8	9.8	9.8
% Assay Phenobarbital Sodium	90.0%-105 %	98.2	98.8	97.7		100.0	99.9	99.9
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND		ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND		ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL		BQL	BQL	BQL
Any other degradation product	NMT 0.2%	0.09	BQL	BQL		0.09	BQL	BQL
Total degradation products	NMT 1.5 %	0.09	BQL	BQL		BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.4	NP	NP		0.3	NP	NP
% Residual Solvent (Tertiary butanol)	To be reported	1.2	0.6	0.8		4.4	2.9	1.7
Note Book Reference		192031-46 to 52	192039-9 to 23			192031-46 to 52	192039-9 to 23	

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

[00174] **Table 32** depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% isopropanol) stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05).

[00175] **Table 32 (65/130 mg/vial, 5% isopropanol, up to 3 months)**

Product Name	Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution prepared in 5% Isopropanol						Date Manufactured:02/21/2019 Date Initiated:09/05/2019	
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)					
Test	Spec.	NPH1966 (65 mg/vial)			NPH1968 (130 mg/vial)			
		Initial DOA: 9/07/2019	3 Months DOA: 12/20/2019		Initial DOA: 9/07/2019	3 Months DOA: 12/20/2019		
			RT	ACC		RT	ACC	
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (65 mg/mL) pH (100 mg/mL) for 130 mg/vial strength	9.2-10.2	9.6	9.6	9.7	9.8	9.7	9.7	
% Assay Phenobarbital Sodium	90.0%-105 %	99.7	98.8	100.0	100.0	101.1	99.1	
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	
Any other degradation product	NMT 0.2%	0.08	BQL	BQL	0.09	BQL	BQL	
Total degradation products	NMT 1.5 %	0.08	BQL	BQL	BQL	BQL	BQL	
Water Content by Karl Fischer	NMT 4.0%	0.3	NP	NP	0.3	NP	NP	
% Residual Solvent (Isopropanol)	To be reported	1.7	0.7	0.7	1.7	1.4	1.4	
Note Book Reference		192031-46 to 52	192039-9 to 23		192031-46 to 52	192039-9 to 23		
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; DOA: Date of analysis ND: Not Detected; NP: Not performed; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea								

[00176] **Table 33** depicts initial results for 65 mg and 130 mg per vial lyophilized phenobarbital sodium from respective bulk solutions containing ethanol or acetonitrile as co-solvent (to obtain 65 mg/ vial, 0.5 mL of the bulk solution was filled in the vials and for 130 mg/ vial strength, 1 ml of the bulk solution was filled in the vials prior to lyophilization). For all test products, 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Notably, unspecified degradation products and total degradation products also remained undetectable or below quantitation limit (0.05%).

[00177] **Table 33 (65/130 mg/vial, acetonitrile or ethanol as co-solvents)**

Test	Spec.	Initial		Initial	
		NPH22035 Formulation in Acetonitrile: Water		NPH22034 Formulation in Ethanol : Water	
		65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)
Description	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	NA	NA	NA	NA
% Assay Phenobarbital Sodium	90.0%-105.0 %	103.6	101.2	100.2	98.3
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	ND	ND	ND	ND
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.4	0.4	0.2	0.2
Residual Solvent	To be reported	NA	NA	3.2	19.2
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea NA: Not available					

[00178] Notably, the results indicated that the above formulations were also storage stable over at least three months as evidenced by all known impurities below quantitation limit as shown in **Tables 31 and 32.** However, an unknown impurity was observed above LOQ level. Interestingly, the residual solvents tertiary butanol and isopropanol were not completely removed after the first cycle of secondary drying. Tertiary butanol and isopropanol were observed above 0.5% in the 65 mg and 130 mg strength products. The same vials were then subjected to additional secondary drying at 25 °C for 30 min and 50 °C for 120 min, and the samples were analyzed for residual solvent after the second cycle of secondary drying.

[00179] After the additional secondary drying steps, residual tert-butanol and isopropanol were observed at lower quantities, respectively. As can be readily seen, the organic solvents could be reduced in quantities, but were not completely removed, possibly suggesting that the tested organic solvents could form a bond in the crystal lattice of phenobarbital. However, further process modifications may possibly result in additional reduction of residual co-solvent, requiring

extensive experimentation. Similar formulations were prepared in organic solvents ethanol and acetonitrile. Here as well, the residual solvent ethanol was not completely removed, but further process modifications may possibly result in additional reduction of residual co-solvent, requiring extensive experimentation.

[00180] Organic solvents such as isopropanol, tertiary butanol, ethanol and acetonitrile were investigated as co-solvents during the lyophilization. Two co solvents tertiary butanol and Isopropanol were used as co-solvents at 5%. The 3M stability data for the formulation with IPA and tert-butanol indicates that although no known degradation products were observed above quantitation limit, the residual solvents could not be removed completely after lyophilization. When ethanol was used as a co solvent similar results were observed. In view of the fact that organic solvents are toxic to all age groups, and in particular to neonates and because residual solvents are typically trapped in the crystal lattice of the Phenobarbital, the lyophilized product with only water as solvent is preferred over formulations containing any organic co solvents.

[00181] X-Ray Powder Diffraction. With reference to **Figs. 5A-5D**, XRPD was performed using the Rigaku Smart-Lab X-ray diffraction system configured for reflection Bragg-Brentano geometry using a line source X-ray beam. The X-ray source is a Cu Long Fine Focus tube that was operated at 40 kV and 44 mA. That source provides an incident beam profile at the sample that changes from a narrow line at high angles to a broad rectangle at low angles. Beam conditioning slits were used on the line X-ray source to ensure that the maximum beam size is less than 10mm both along the line and normal to the line. The Bragg-Brentano geometry is a para-focusing geometry controlled by passive divergence and receiving slits with the sample itself acting as the focusing component for the optics. The inherent resolution of Bragg-Brentano geometry is governed in part by the diffractometer radius and the width of the receiving slit used. Typically, the Rigaku Smart-Lab is operated to give peak widths of 0.1 °2θ or less. The axial divergence of the X-ray beam is controlled by 5.0-degree Soller slits in both the incident and diffracted beam paths. The samples were placed in a low-background, silicon holder using light manual pressure to keep the sample surfaces flat and level with the reference surface of the holder. The samples were analyzed from 2 to 40 °2θ using a continuous scan of 6 °2θ per minute with an effective step size of 0.02 °2θ.

[00182] The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the full scope of the present disclosure and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claimed invention.

[00183] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the full scope of the concepts disclosed herein. The disclosed subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C ... and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

CLAIMS

What is claimed is:

1. A pharmaceutical product, comprising:
   a container enclosing a single dose of lyophilized phenobarbital sodium powder;
   wherein the phenobarbital sodium powder optionally contains residual quantities of tert-butanol, isopropanol, ethanol, or acetonitrile and wherein the phenobarbital sodium powder otherwise does not contain an organic solvent or preservative; and
   wherein the phenobarbital sodium powder is storage-stable.

2. The product of claim 1, wherein the single dose phenobarbital sodium powder is a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose.

3. The product of claim 1, wherein the container is a single use glass vial.

4. The product of claim 1, wherein the container is a 10 ml vial.

5. The product of claim 1, wherein the single dose, upon reconstitution with water for injection, has a pH range of between 9.2 and 10.2.

6. The product of claim 1, wherein the lyophilized phenobarbital sodium powder contains, after storage at 25 °C and 60% relative humidity for 6 months, less than 2.0% water as determined by Karl Fischer test.

7. The product of claim 1, wherein the lyophilized phenobarbital sodium powder contains, after storage at 25 °C and 60% relative humidity for 6 months, less than 1.8% water as determined by Karl Fischer test.

8. The product of claim 1, wherein the lyophilized phenobarbital sodium powder contains, after storage at 25 °C and 60% relative humidity for 6 months, less than 1.6% water as determined by Karl Fischer test.

9. The product of claim 1, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 6 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution

with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

10. The product of claim 1, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 12 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

11. The product of claim 1, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 15 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

12. The product of claim 1, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 24 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

13. The product of claim 1, wherein the lyophilized amorphous phenobarbital further comprises NaCl.

14. The product of claim 1, wherein the single dose phenobarbital sodium powder is a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose, and wherein the container is a single use glass vial.

15. The product of claim 14, wherein the lyophilized phenobarbital sodium powder contains, after storage at 25 °C and 60% relative humidity for 6 months, less than 2.0% water as determined by Karl Fischer test.

16. The product of claim 15, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 6 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

17. The product of claim 15, wherein the lyophilized phenobarbital sodium powder is storage-stable such that, after storage at 25 °C and 60% relative humidity for 12 months, equal or less than 0.05% of total degradation products from the phenobarbital are detectable upon reconstitution with water in the reconstituted solution, and wherein the degradation products include 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

18. The product of claim 1, wherein the lyophilized phenobarbital sodium powder is lyophilized using a step of freezing to a temperature of about -50 °C, a primary drying step at a pressure of between about 50mTorr and 75 mTorr and at a temperature of between about -50 °C and about 0 °C, and a secondary drying step at a pressure of between about 50 mTorr and 75 mTorr and at a temperature of between about 25 °C and about 50 °C.

19. The product of claim 18, wherein the step of freezing is performed without application of a vacuum.

20. The product of claim 18, wherein the primary drying step is performed over a period of at least 1,000 minutes and/or wherein the secondary drying step is performed over a period of at least 200 minutes.

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.

Fig. 1A

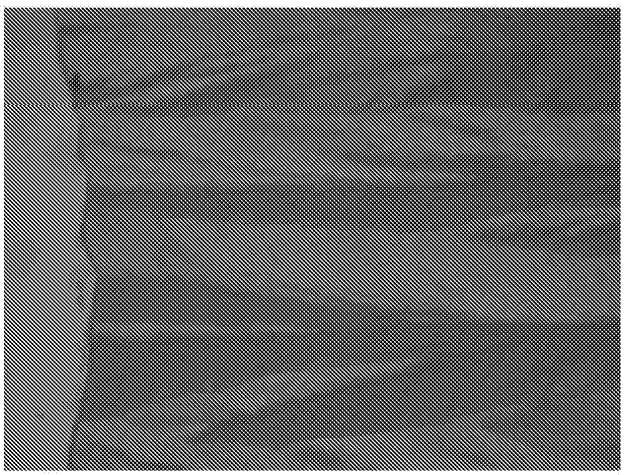


Fig. 1B

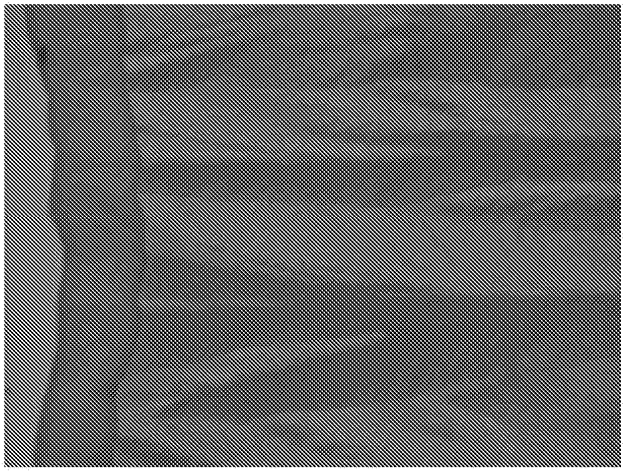


Fig. 1C

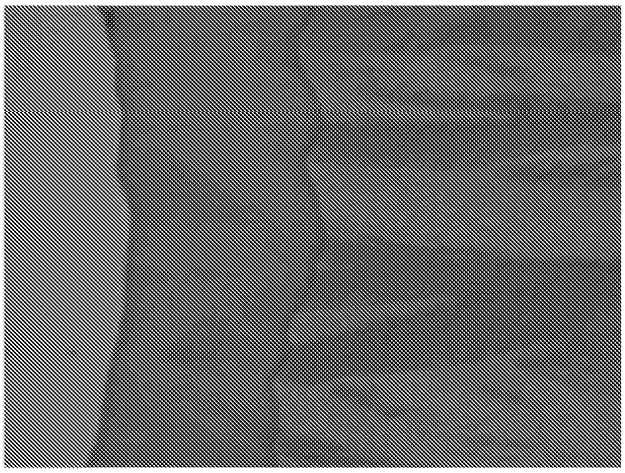


Fig. 1D

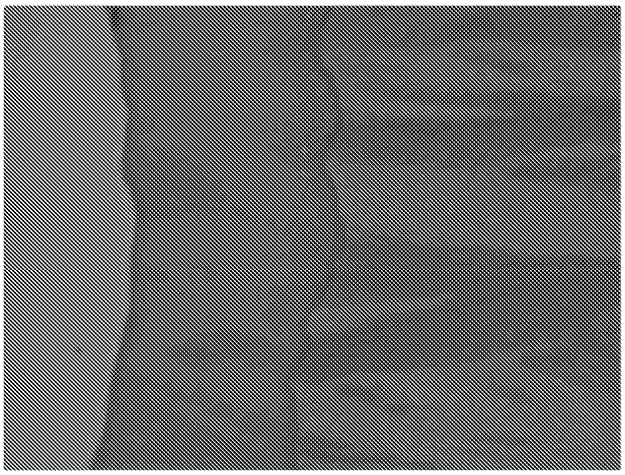


Fig. 1E

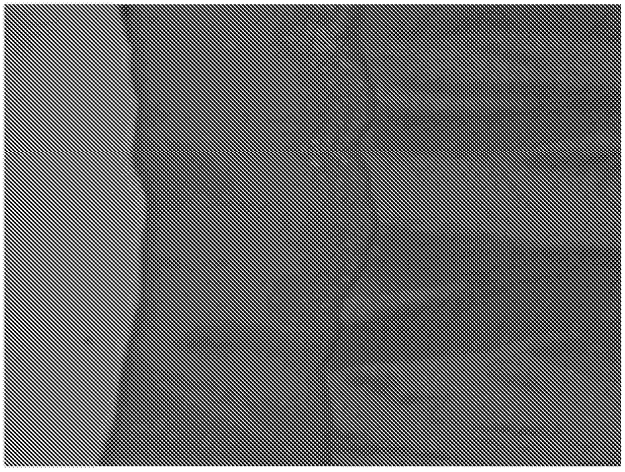


Fig. 1F

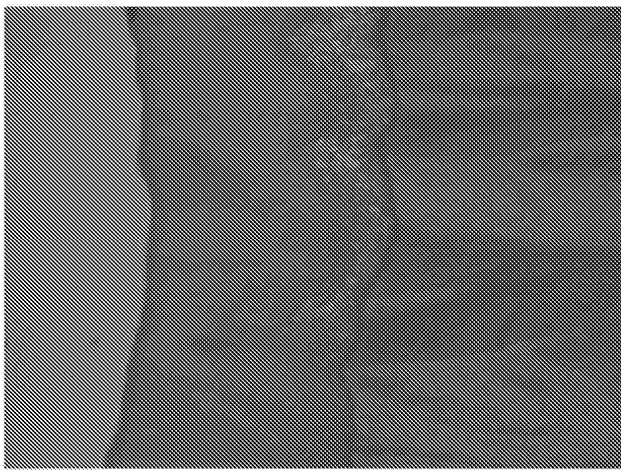


Fig. 2A

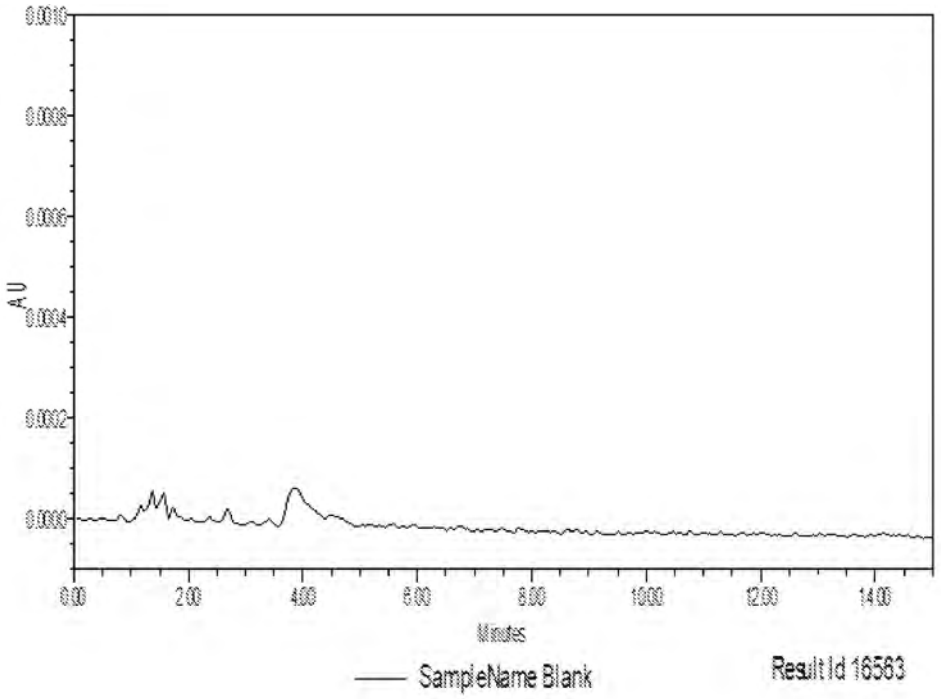
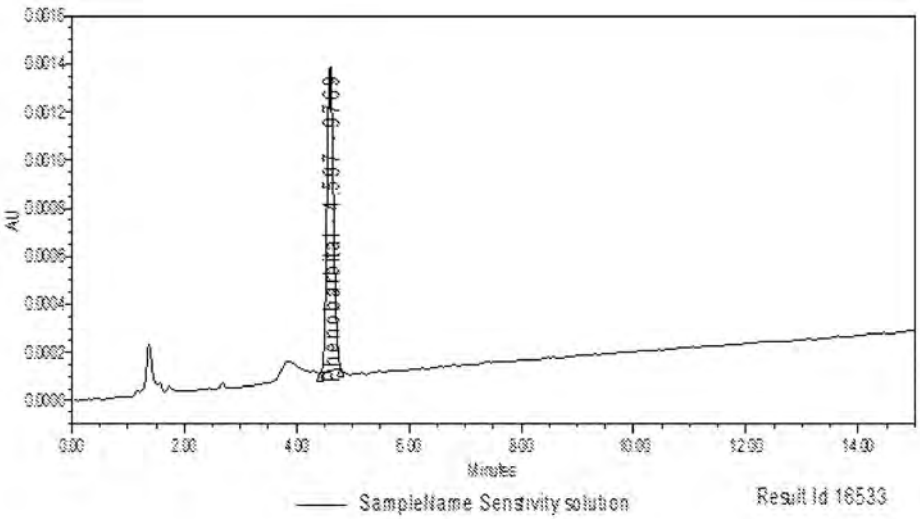
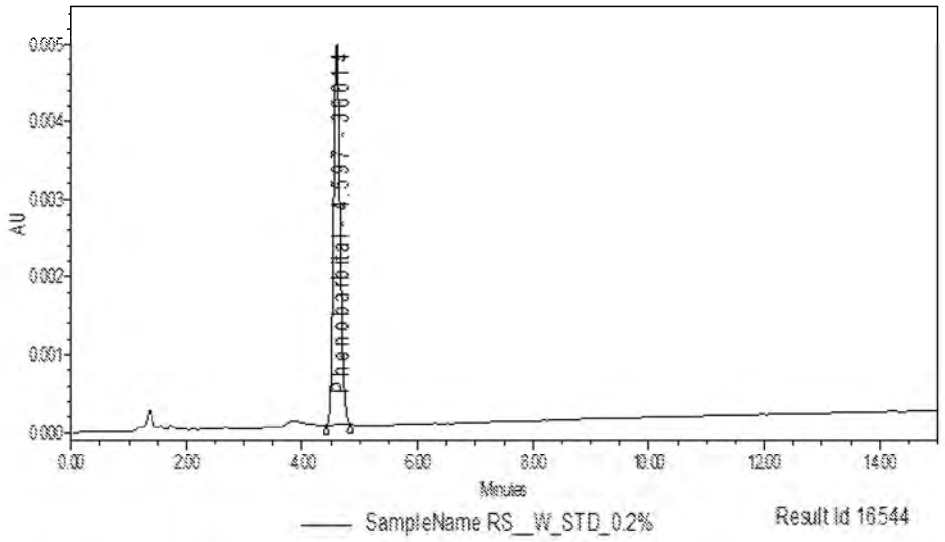

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0.0002
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14.00
Minutes
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Result Id 16563

Fig. 2B



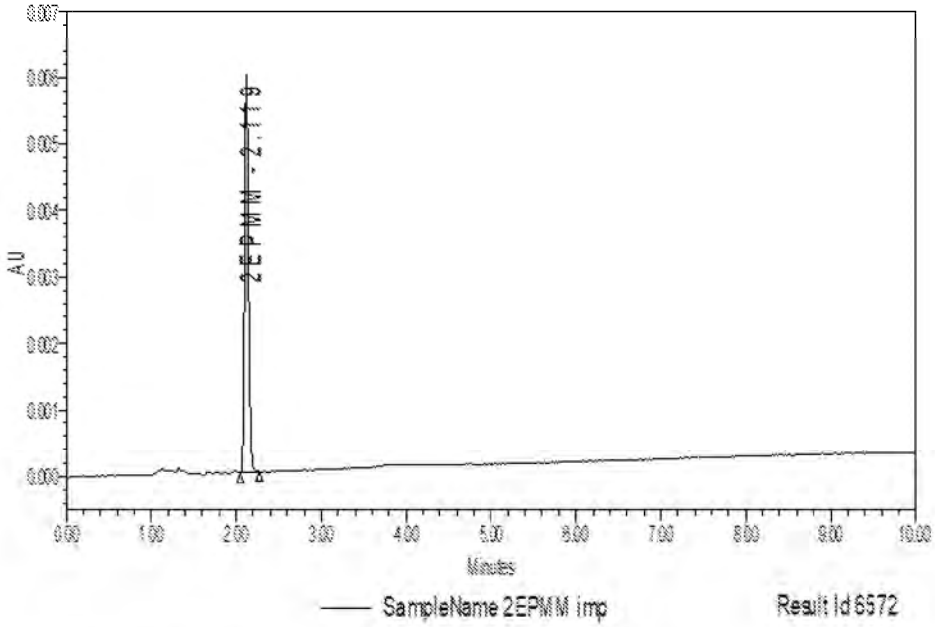
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7861.1	1.1

Fig. 2C



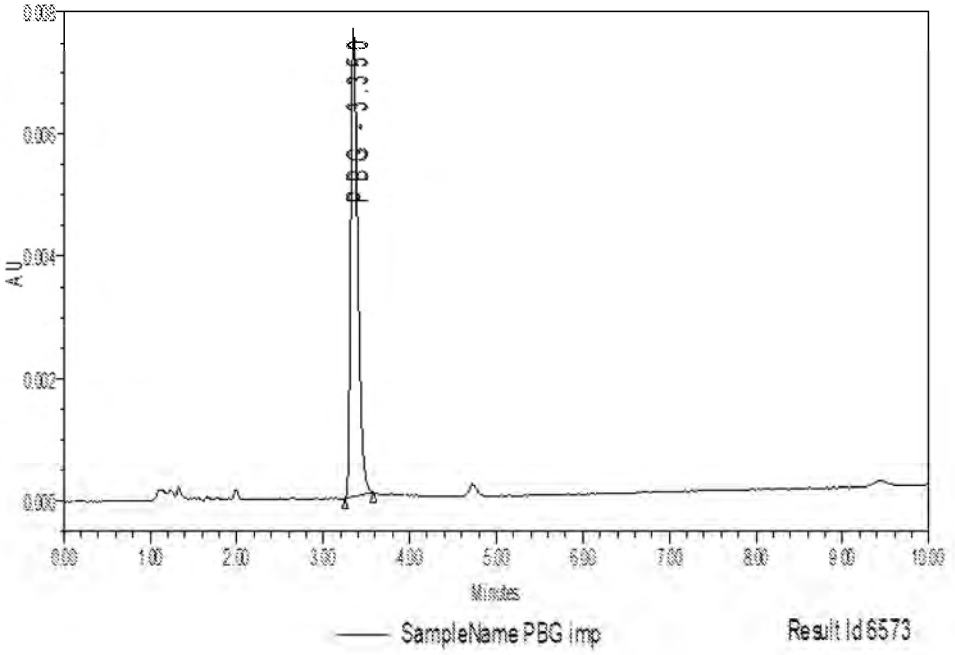
	Peak Name	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	sh	USP Plate Count	USP Tailing	PurityM Angle	PurityM Threshold
1	2EPMM	2.119	18797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	PBG	3.350	41778	100.00	2093	8801.9	1.5	21.648	62.982

Fig. 2F

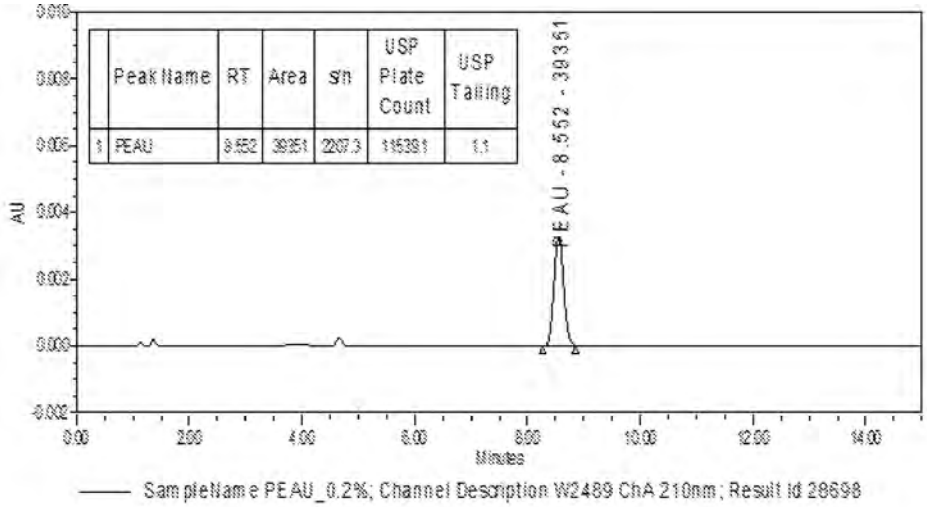

Peak Name
RT
Area
s/n
USP Plate Count
USP Tailing
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39351
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PEAU - 8.552 - 39351
AU
Minutes
SampleName PEAU_0.2%; Channel Description W2489 ChA 210nm; Result id 28698

Fig. 2G

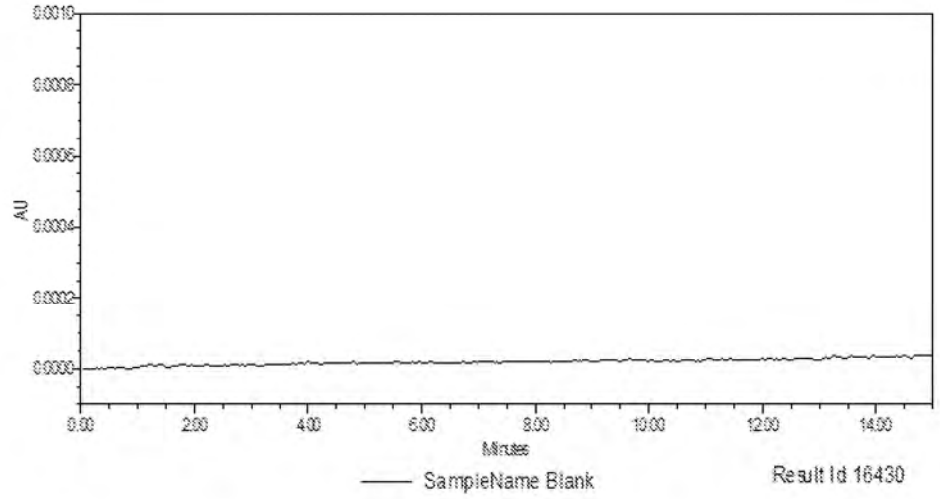
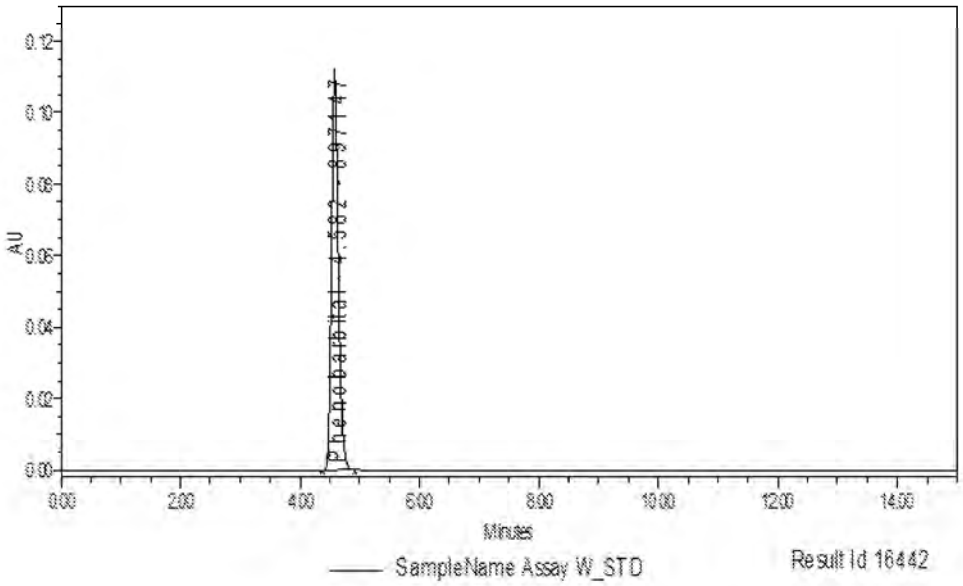
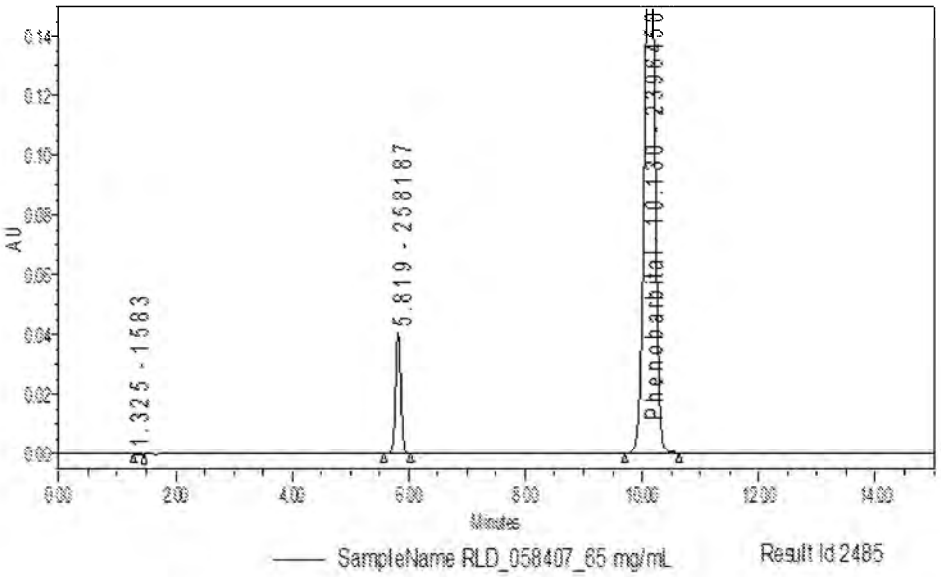

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Fig. 2H



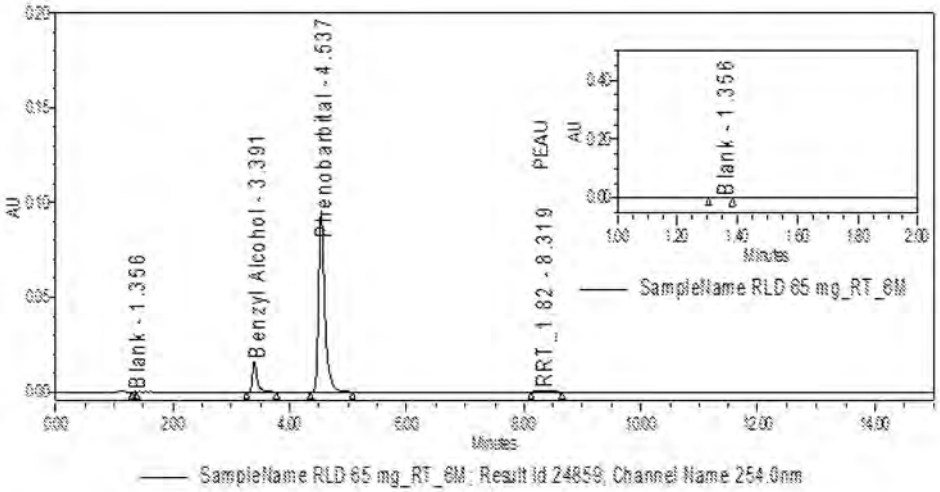
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



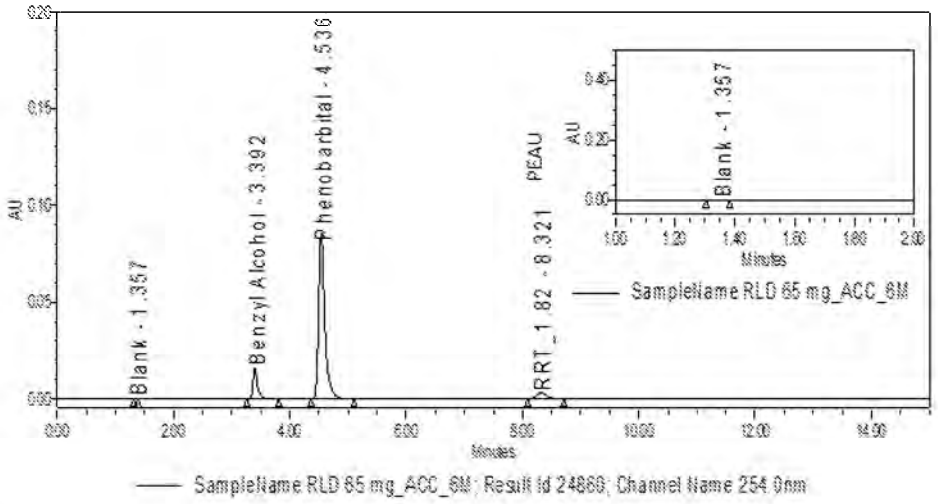
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



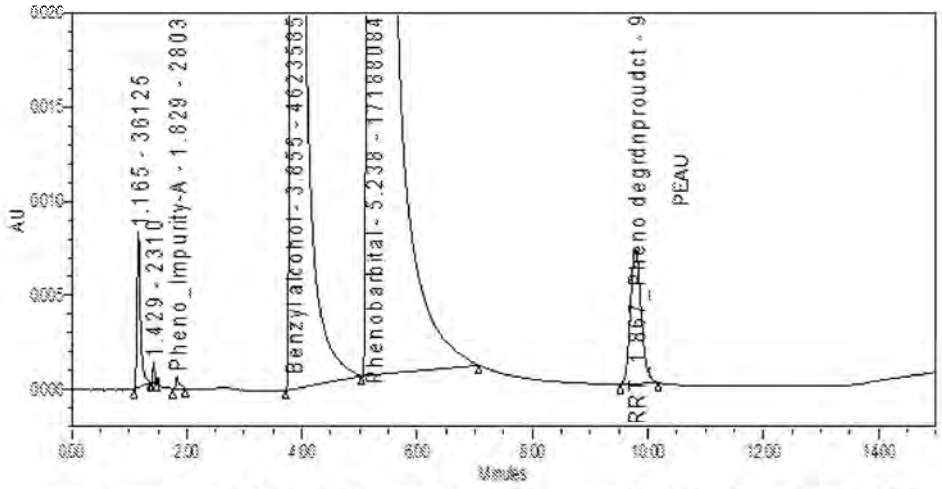
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



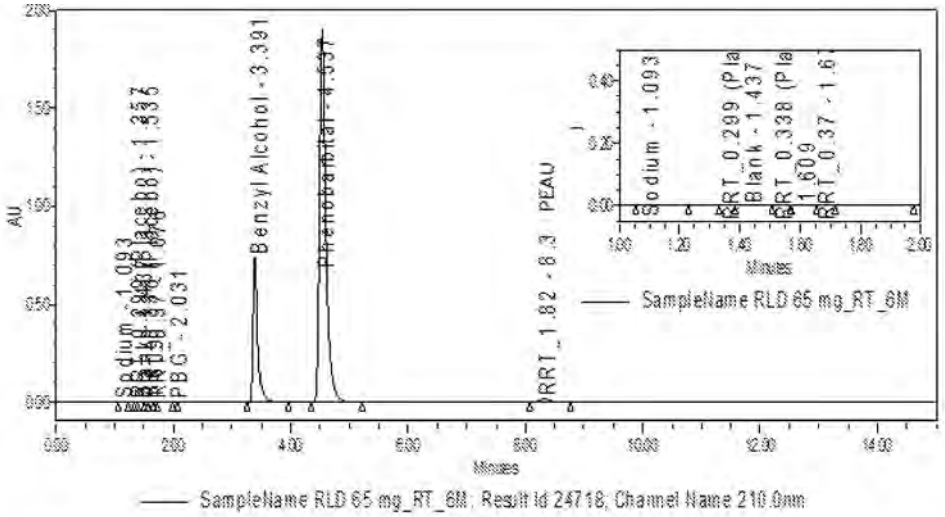
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627536	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

Fig. 3D



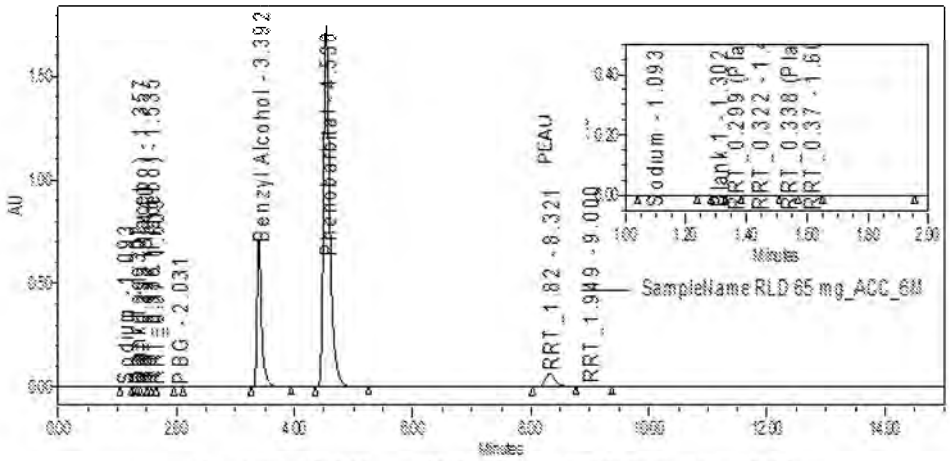
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.97	17.1	390.1	12312.8	1.5
2	Pheno_Impurity-A	1.829	2803	0.01	5.2	0.3	7608.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1016.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92997	0.42	16.5	3.5	13191.5	1.2

Fig. 3E



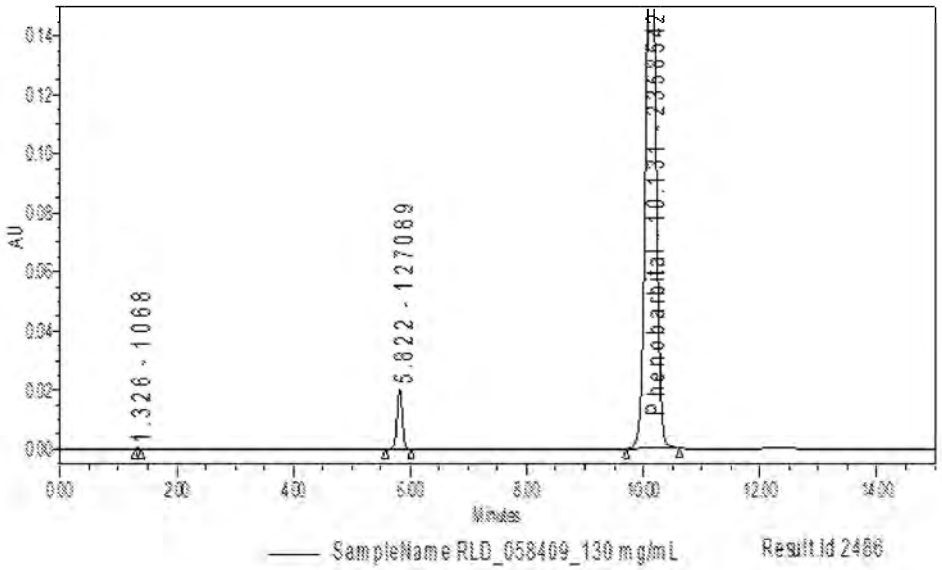
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



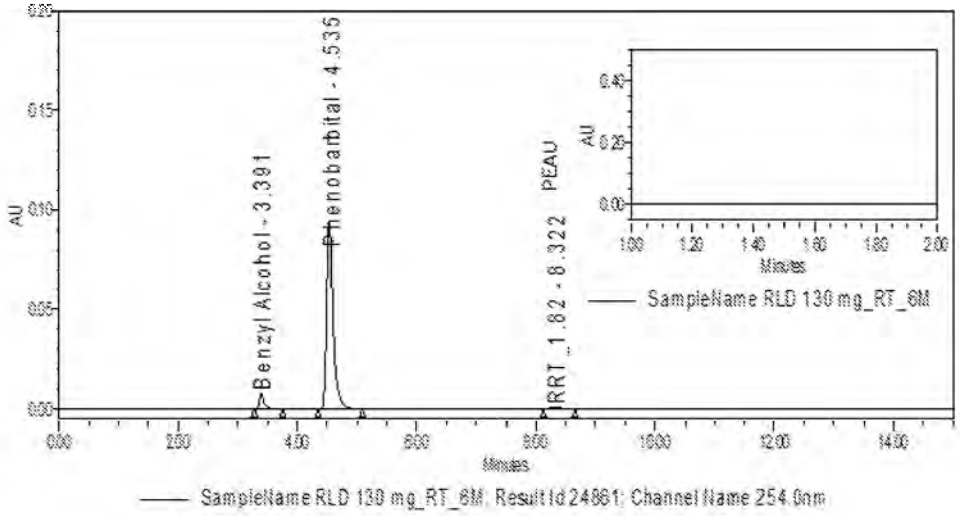
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



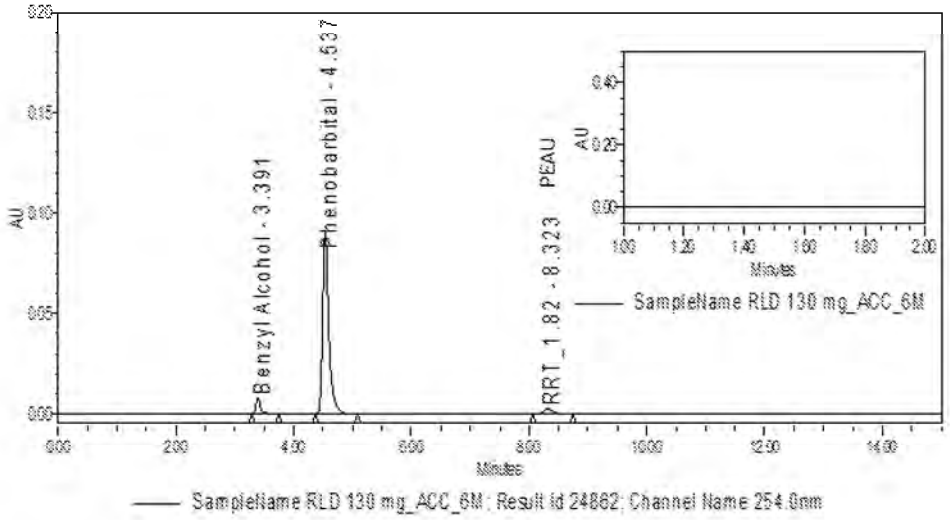
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



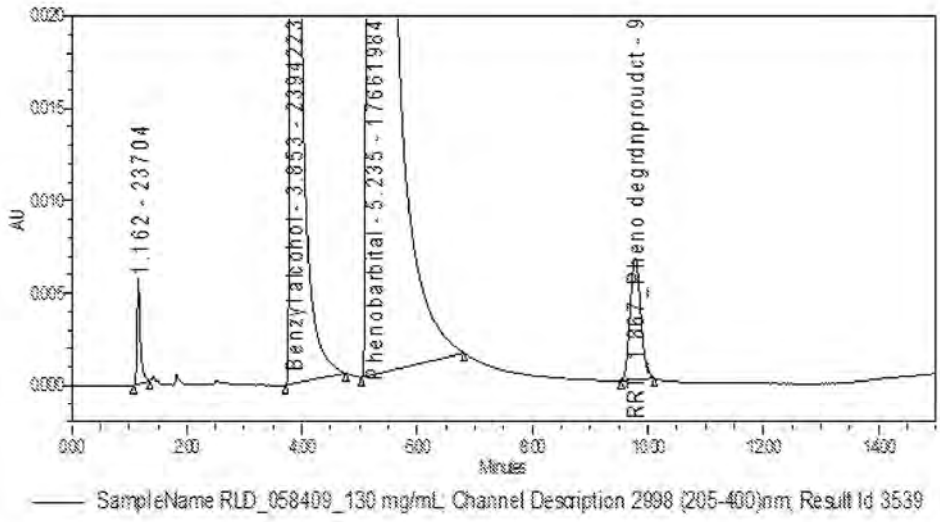
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7887	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



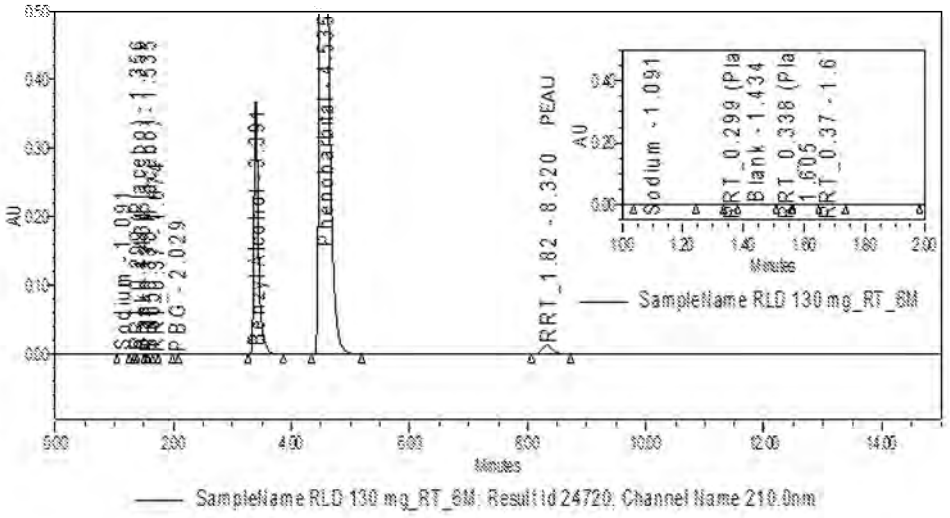
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



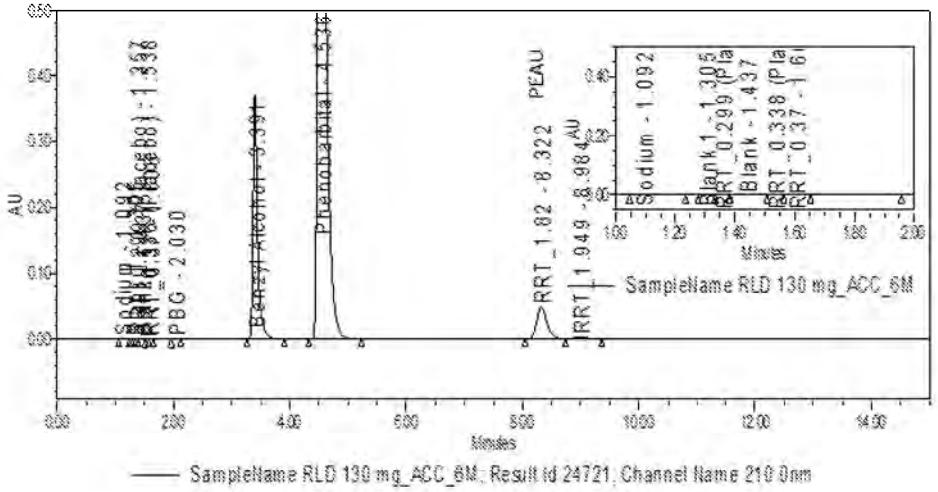
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3853	2394223	11.87	20.8	223.9	12438.0	1.5
2	Phenobarbital	5.235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Pheno degrdnproudct	9.776	83640	0.41	16.6	3.5	19612.7	1.1

Fig. 3K



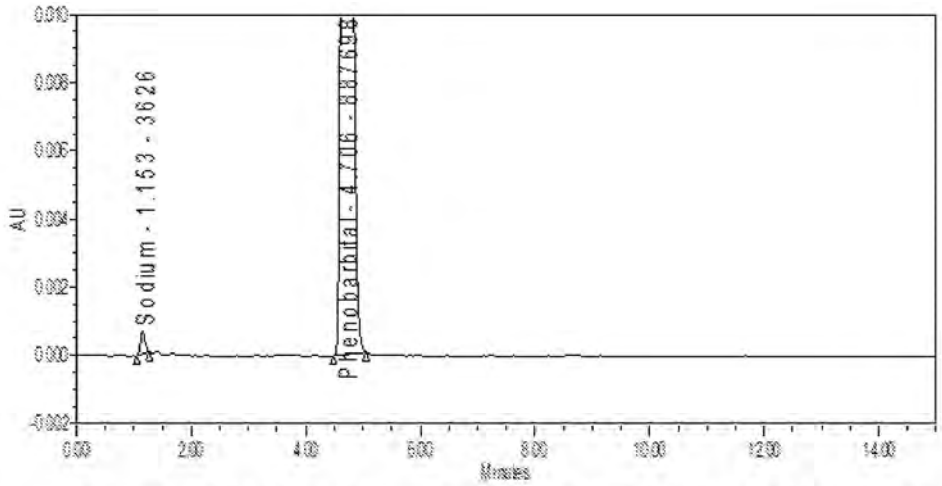
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.329	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594816	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

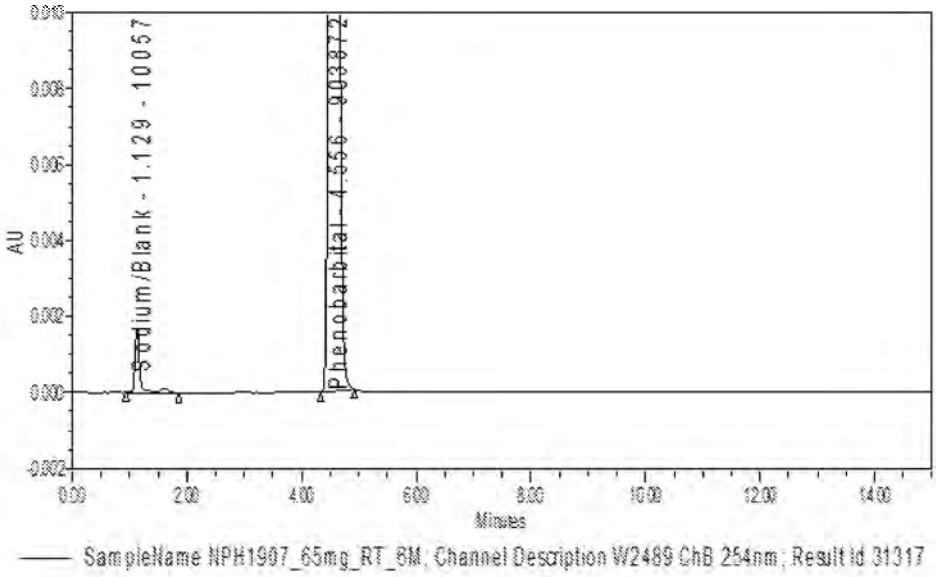
Fig. 4A



SampleName #NPH1907_Lyo_65mg/mL_Initial. Channel Description W2489 ChB 254nm; Result Id 13991

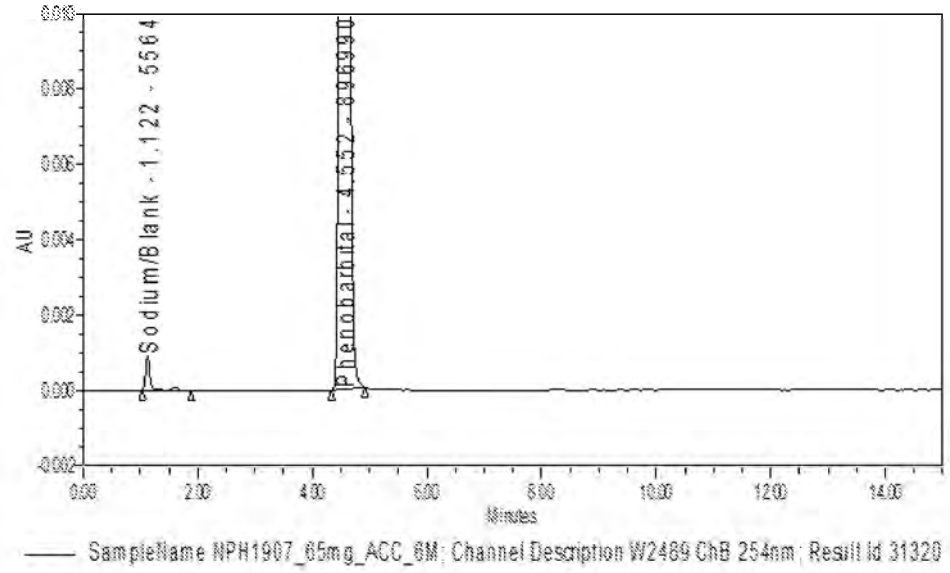
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887598	58.856	mg/mL	99.1	19.3	52843.5	7982.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

Fig. 4B



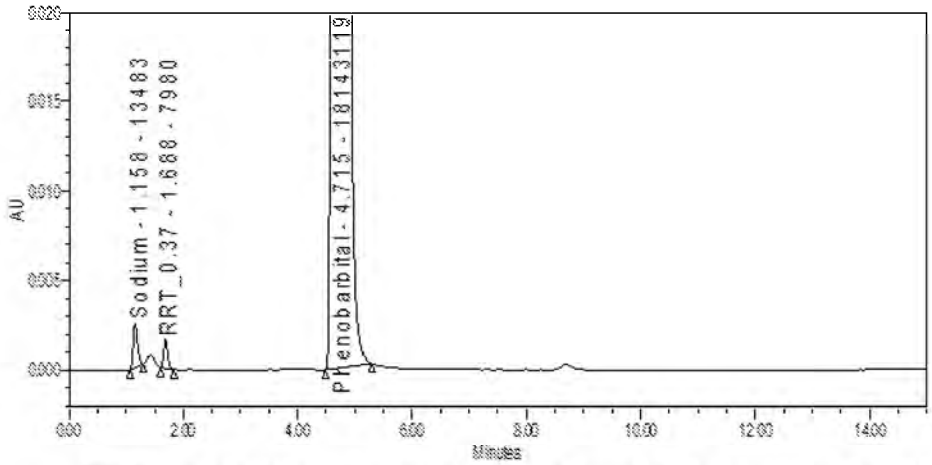
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.388	mg/mL	100.0	20.8	44622.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

Fig. 4C



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	896990	58.956	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1235.7	1.3

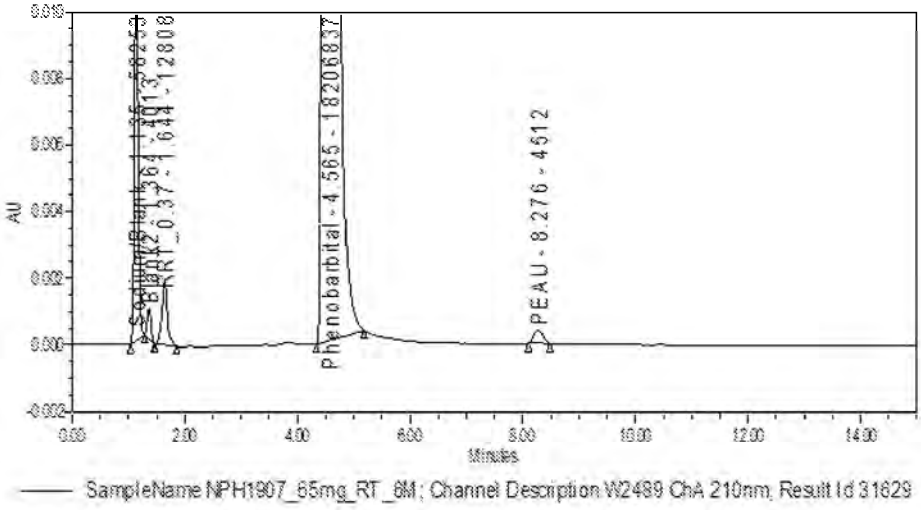
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial, Channel Description W2489 ChA 210nm, Result Id 14043

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.88	58.872	mg/mL	17.3	1073191.3	7604.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.025	mg/mL	3.7	772.4	2602.8	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1039.2	1.2

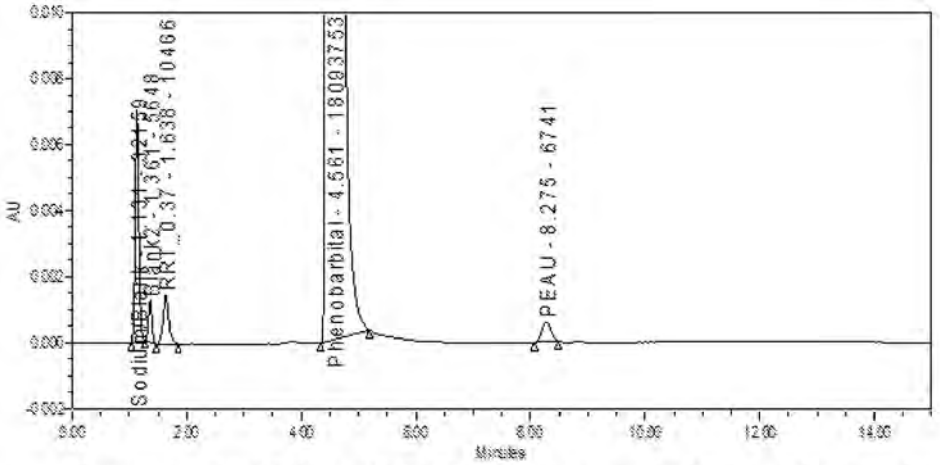
Fig. 4E



SampleName NPH1907_65mg_RT_6M; Channel Description W2489 ChA 210nm; Result Id 31629

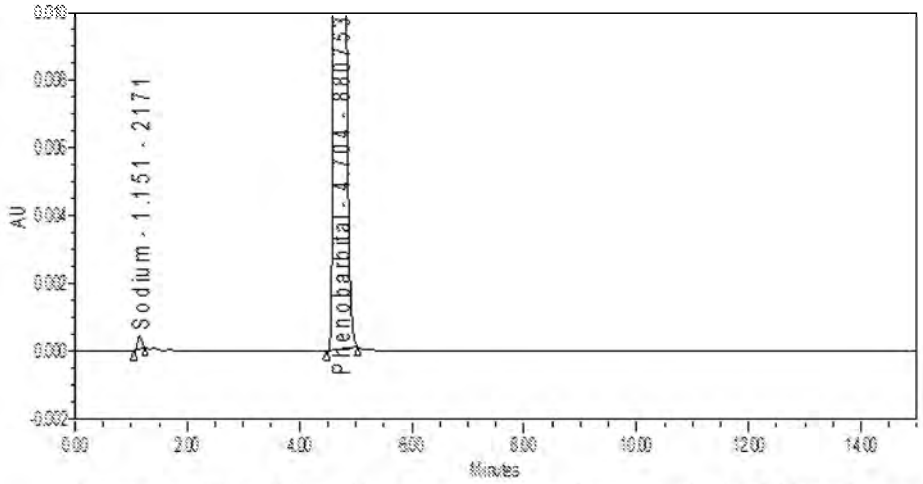
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4013	0.02			1.9	625.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	279.0	12299.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	1518675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	SodiumBlank	1.135	58253	0.32	0.173	mg/mL		6406.1	1363.0	1.1

Fig. 4F



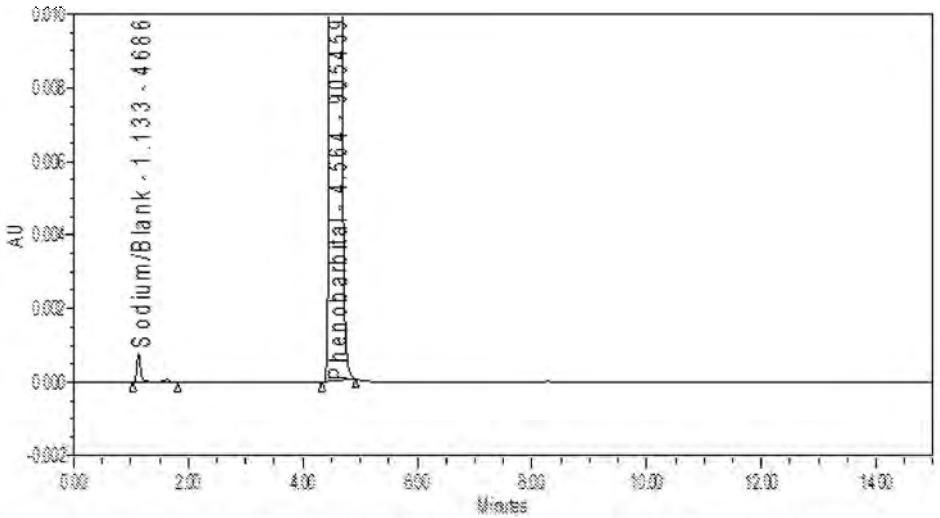
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.391	5648	0.03			1.9	599.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.5	427.7	11916.8	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1693108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1084.2	1482.5	1.1
5	SodiumBlank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

Fig. 4G



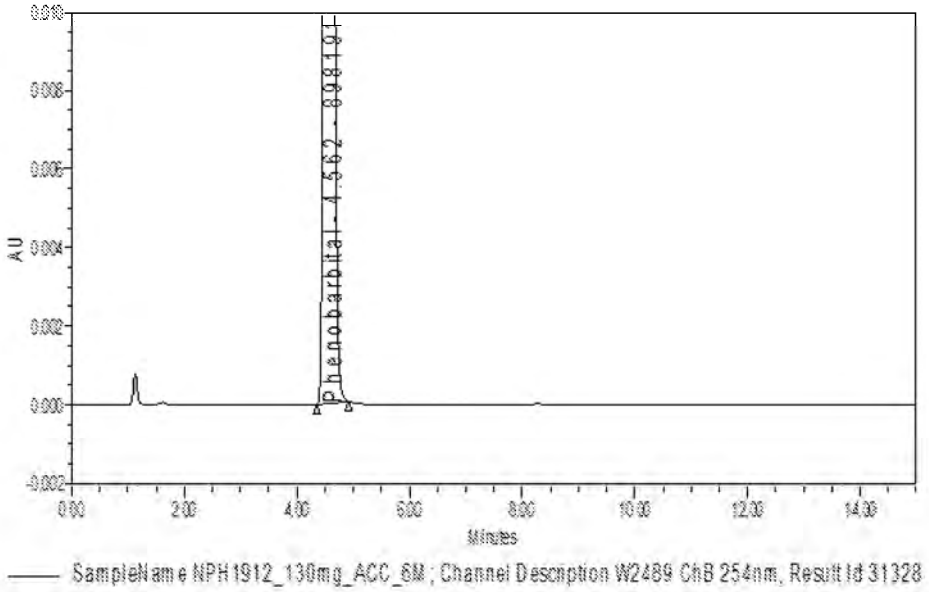
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	888753	116.796	mg/mL	98.3	19.3	40192.1	7866.8	1.2
2	Sodium	1.151	2171					149.3	959.0	1.0

Fig. 4H



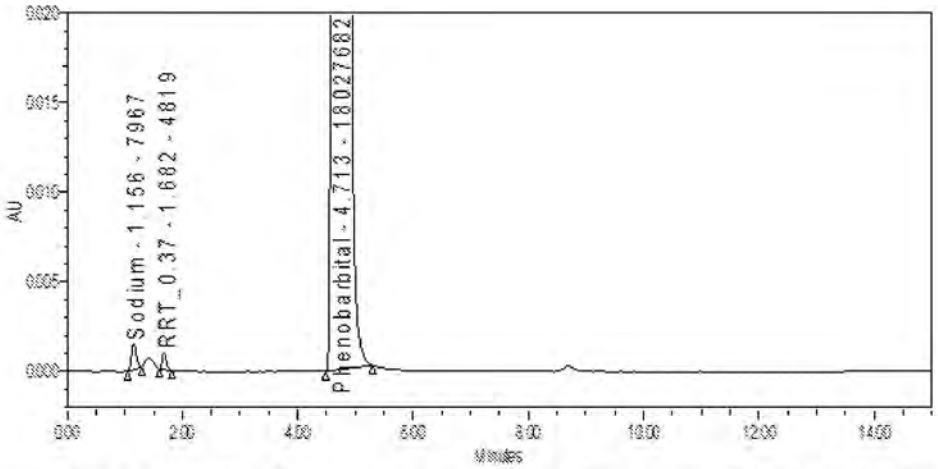
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	116.995	mg/mL	100.2	20.7	55858.2	8539.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			359.4	1316.2	1.4

Fig. 4I



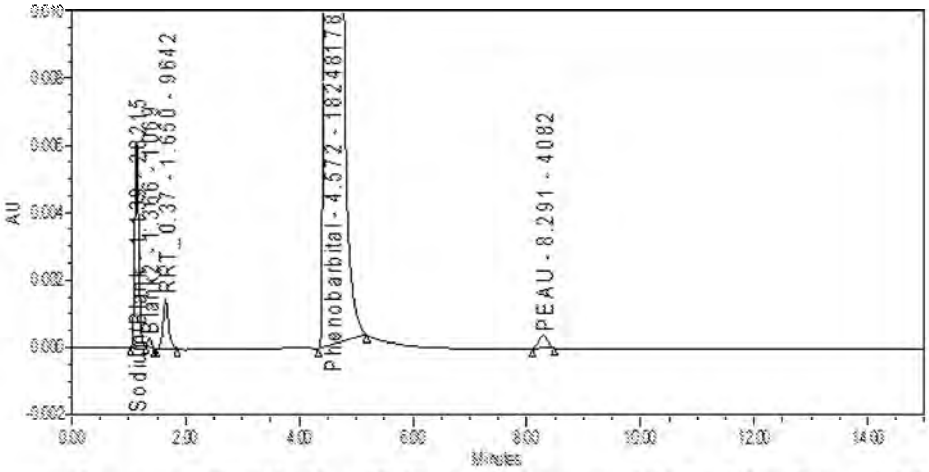
	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898191	118.035	mg/mL	99.4	553756	8686.8	1.1

Fig. 4J



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.395	mg/mL	17.0	1001025.6	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	433.7	2491.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

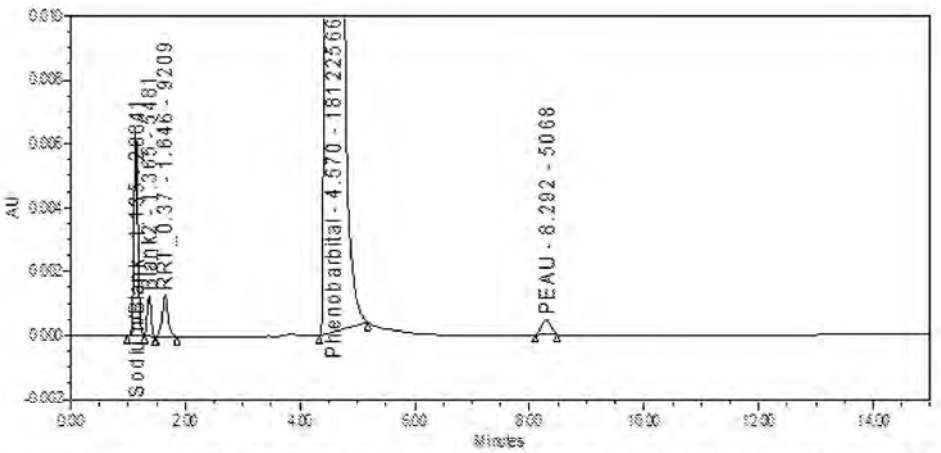
Fig. 4K



SampleName NPH1912_130mg_RT_6M; Channel Description W2489 ChA 210nm; Result Id 31637

	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.6	1.0
3	Phenobarbital	4.572	18248178	99.76	106.167	mg/mL	15.9	13735022.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	2.0	632.7	1918.4	1.1
5	SodiumBlank	1.139	28215	0.15	0.167	mg/mL		3438.2	1382.8	1.1

Fig. 4L



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChA 210nm; Result Id 31640

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.365	548	0.03			1.9	587.2	2149.1	1.1
2	PEAU	8.292	5068	0.03	0.030	mg/mL	14.5	256.0	12335.6	1.0
3	Phenobarbital	4.570	18122566	99.73	107.442	mg/mL	15.1	1028658.2	6830.4	1.1
4	RRT_0.37	1.646	9209	0.05	0.055	mg/mL	1.9	725.3	1481.9	1.1
5	Sodium/Blank	3.135	28641	0.16	0.171	mg/mL		3440.5	1382.6	1.1

Fig. 5A

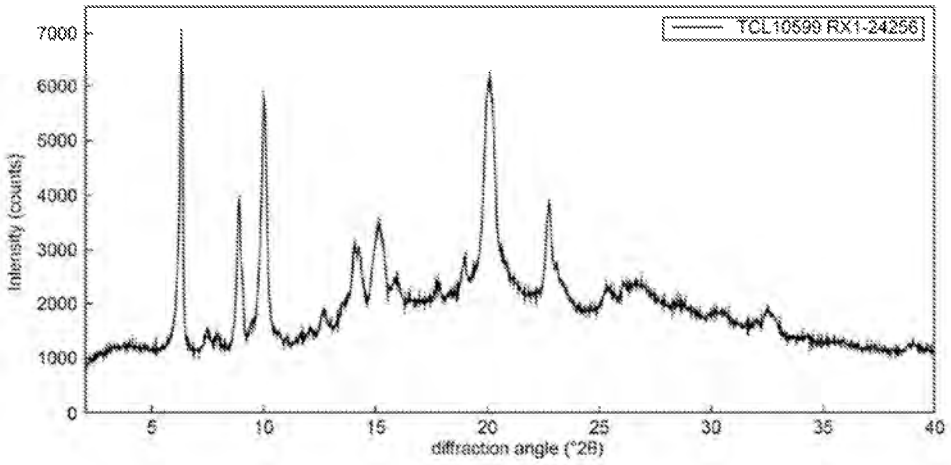

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2000
1000
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5B

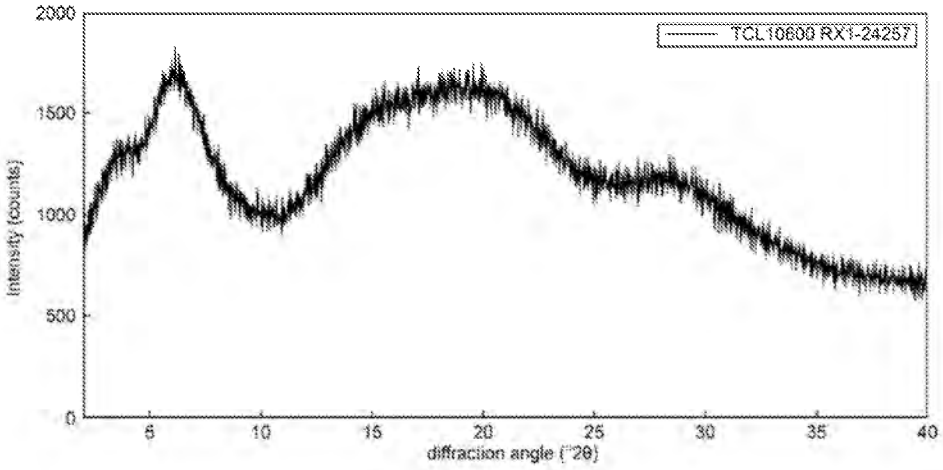

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1500
1000
500
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Intensity (counts)
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20
25
30
35
40
diffraction angle (°2θ)

Fig. 5C

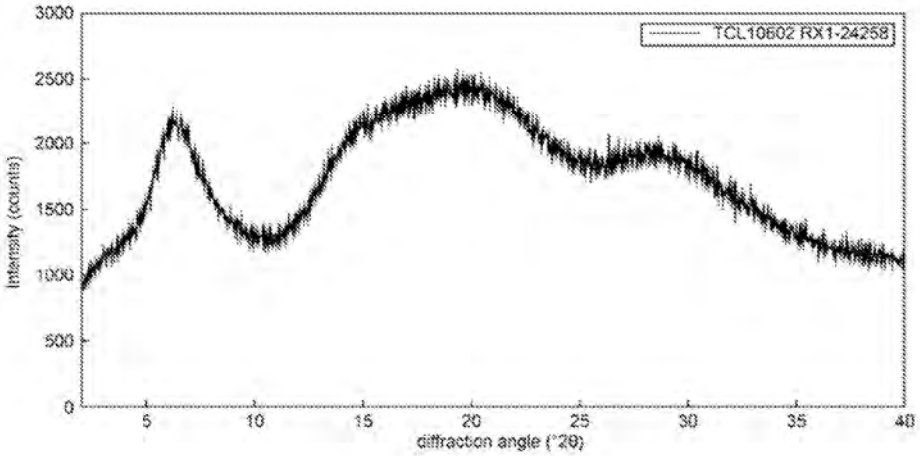

TCL10602 RX1-24258
Intensity (counts)
diffraction angle (°2θ)
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1500
2000
2500
3000
5
10
15
20
25
30
35
40

Fig. 5D

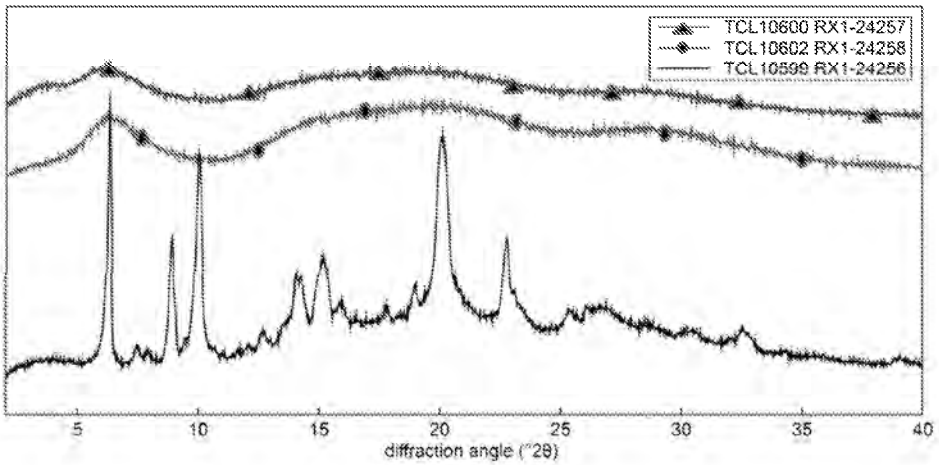

TCL10600 RX1-24257
TCL10602 RX1-24258
TCL10599 RX1-24256
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10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 1A



Fig. 1B

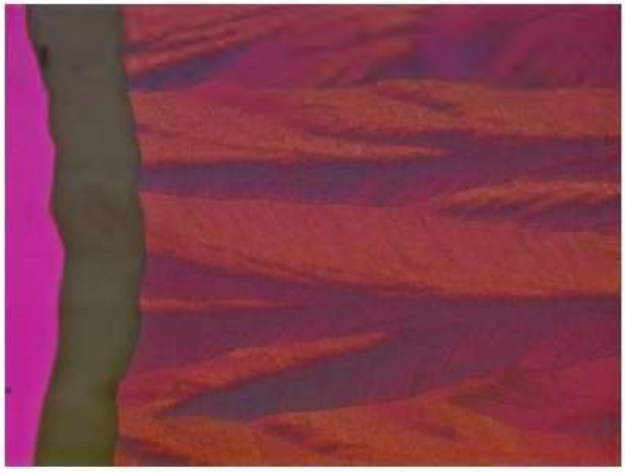


Fig. 1C



Fig. 1D



Fig. 1E

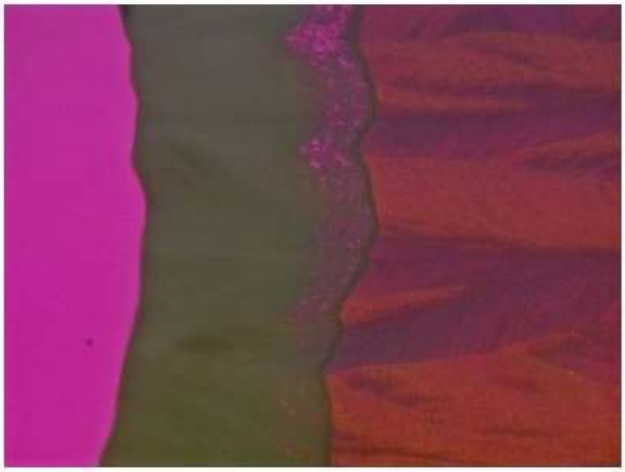


Fig. 1F

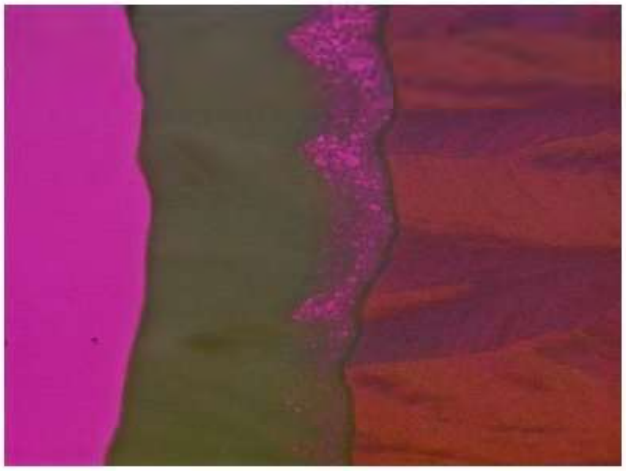


Fig. 2A

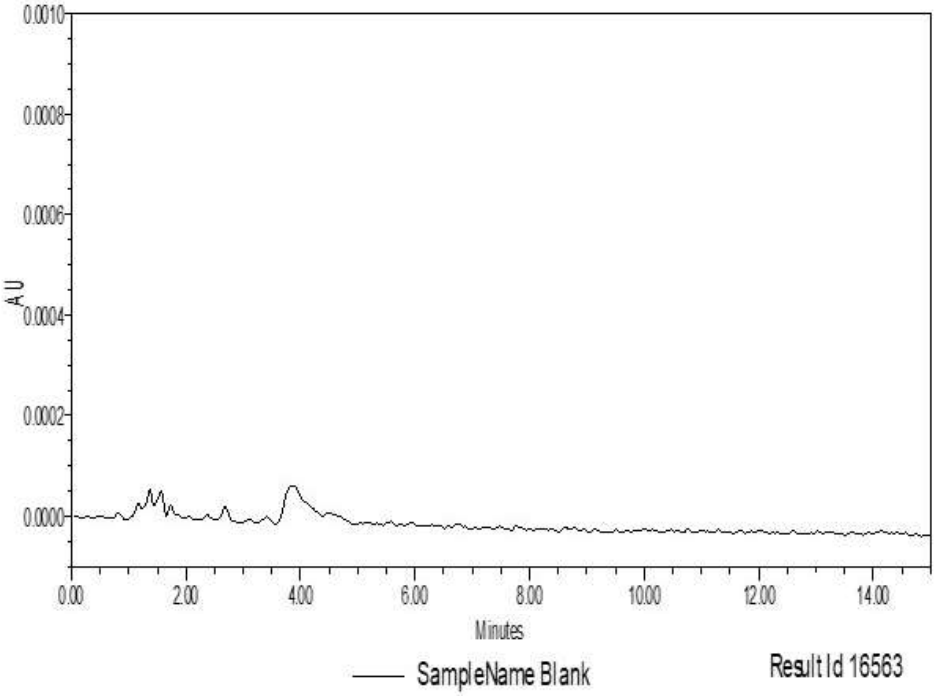
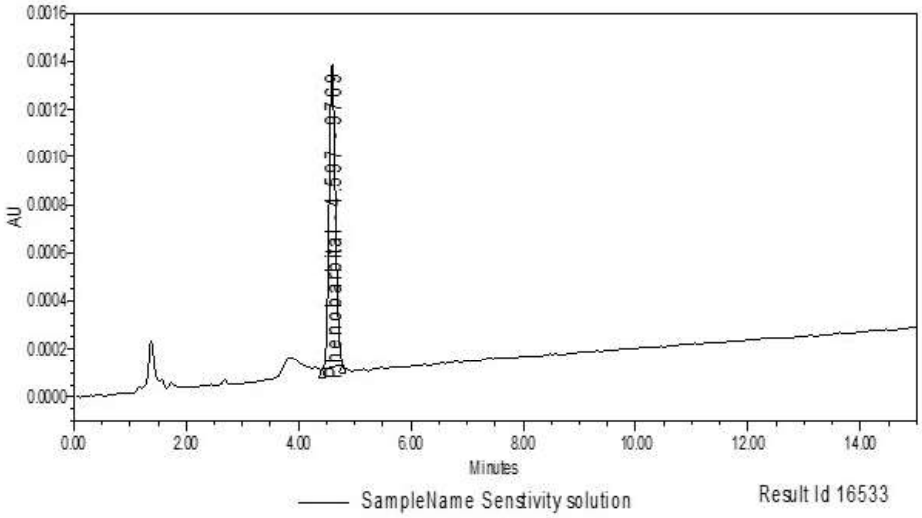
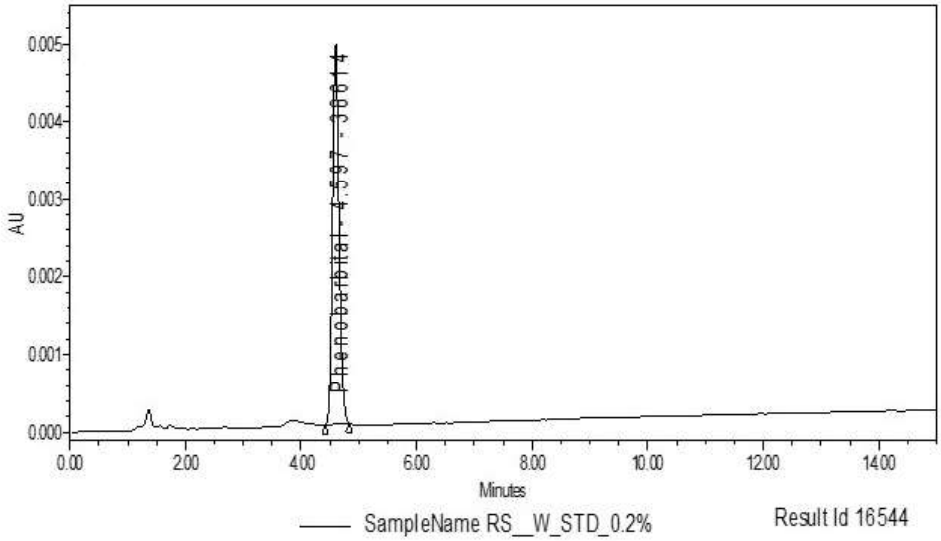

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Minutes
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Result Id 16563

Fig. 2B



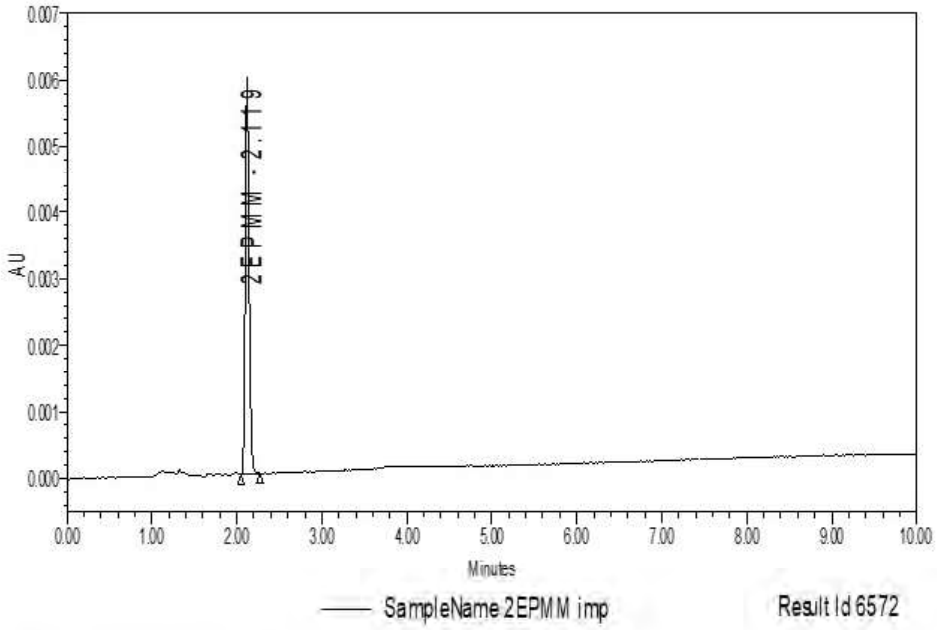
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7861.1	1.1

Fig. 2C



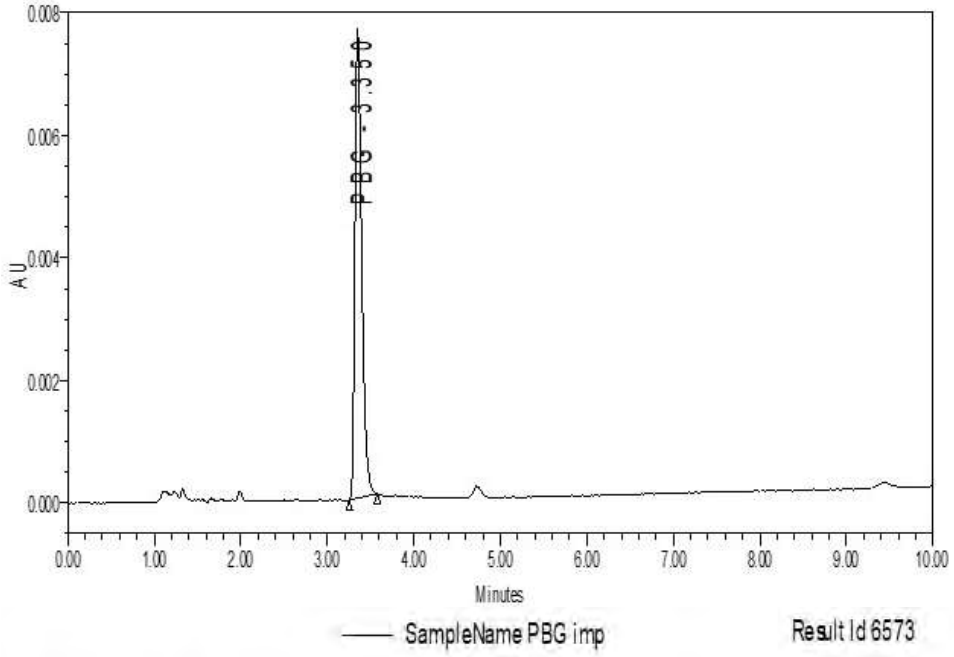
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	2EPMM	2.119	18797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	% Area	s/h	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	PBG	3.350	41776	100.00	2090	8801.9	1.5	21.648	62.982

Fig. 2F

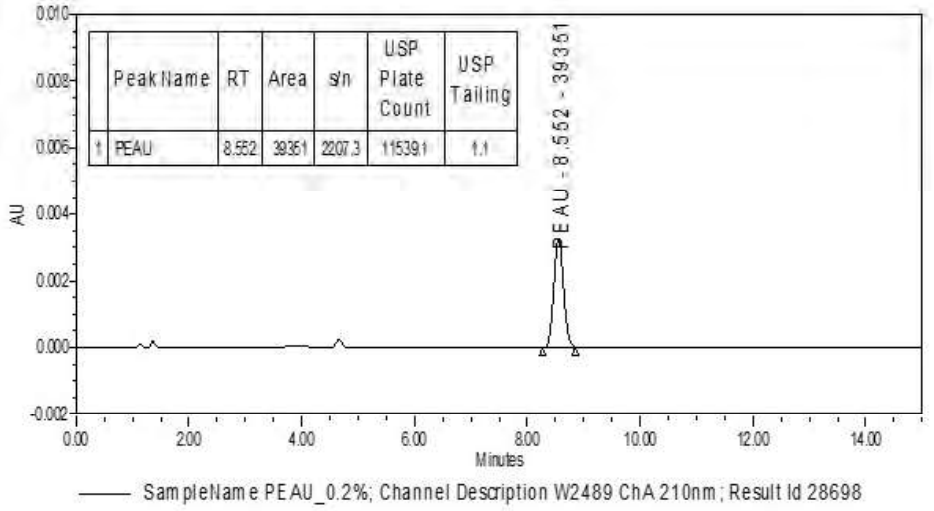

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6.00
8.00
10.00
12.00
14.00
Minutes
PEAU - 8.552 - 39351
Peak Name | RT | Area | s/n | USP Plate Count | USP Tailing
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SampleName PEAU_0.2%; Channel Description W2489 ChA 210nm; Result Id 28698

Fig. 2G

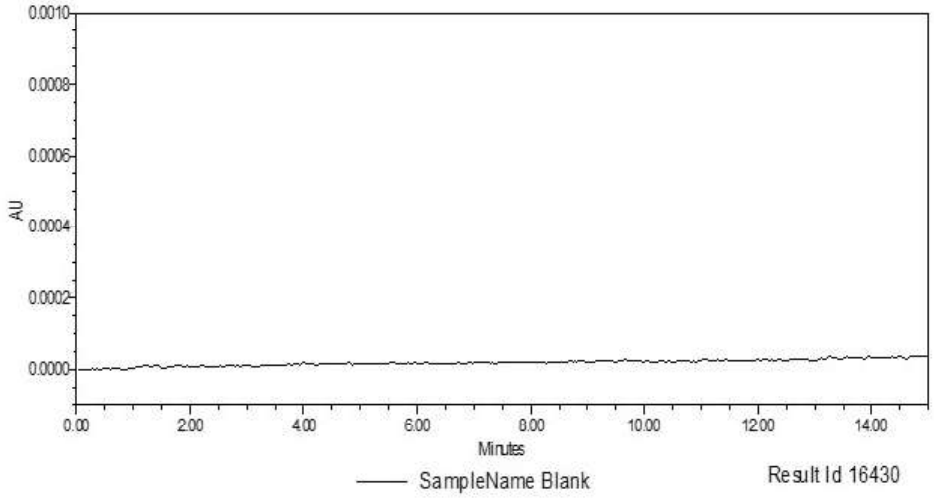
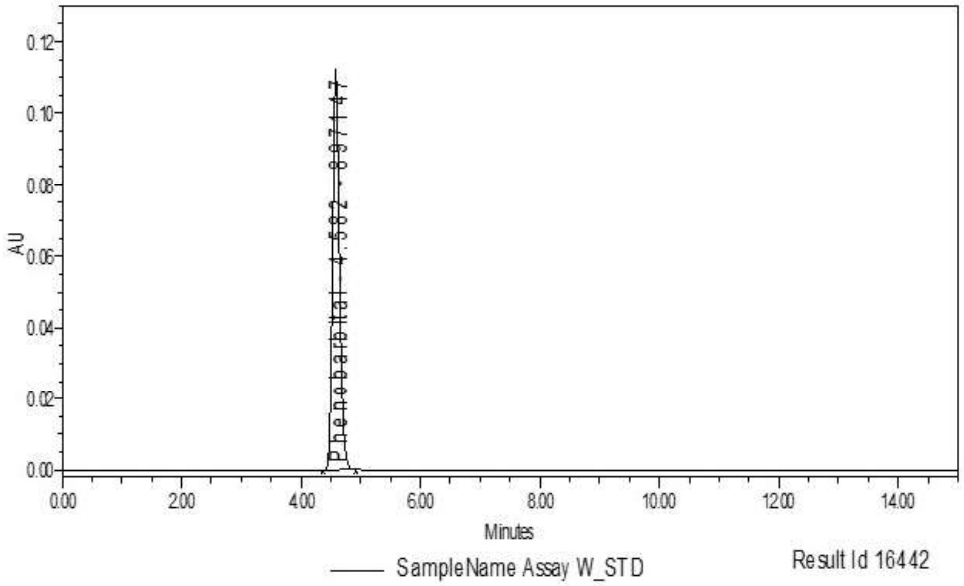
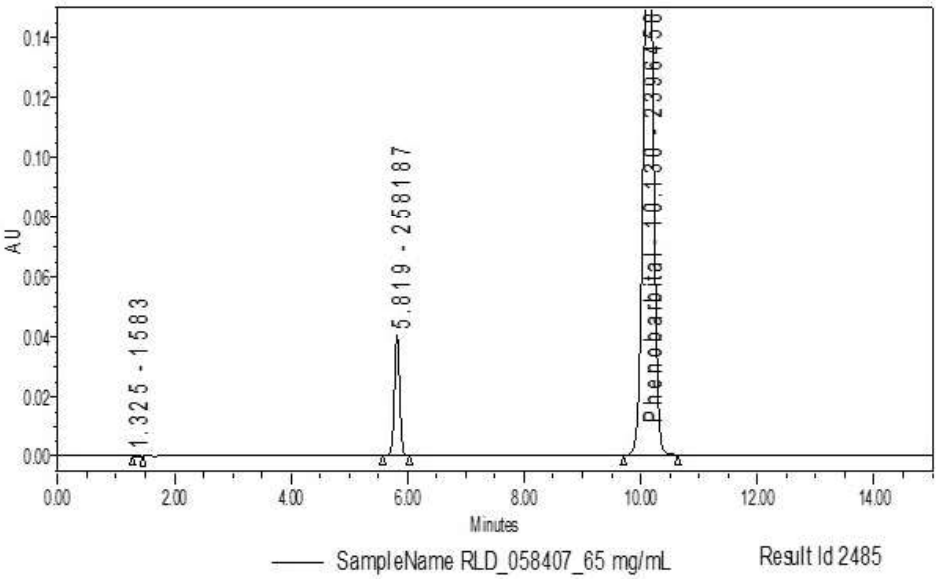

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Fig. 2H



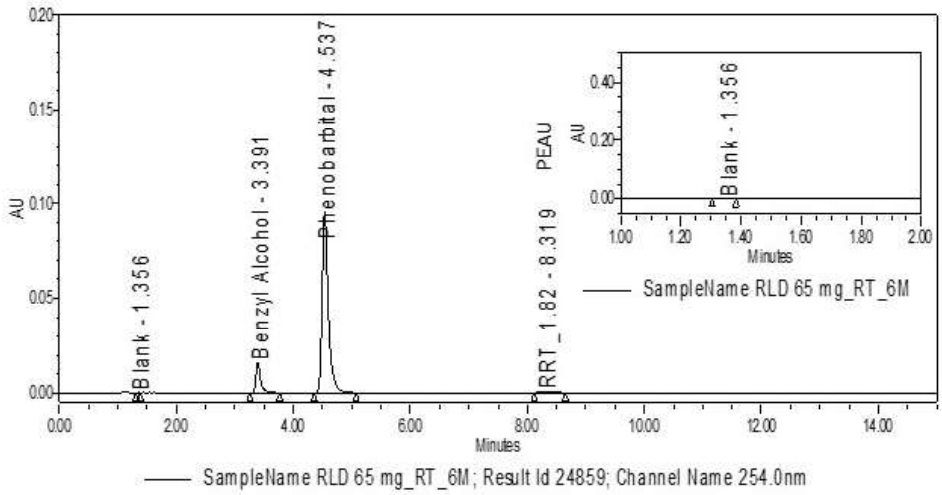
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



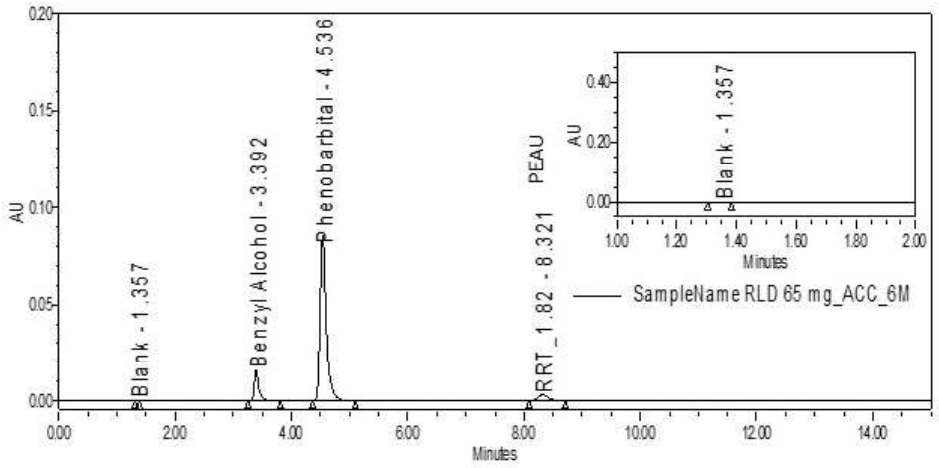
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



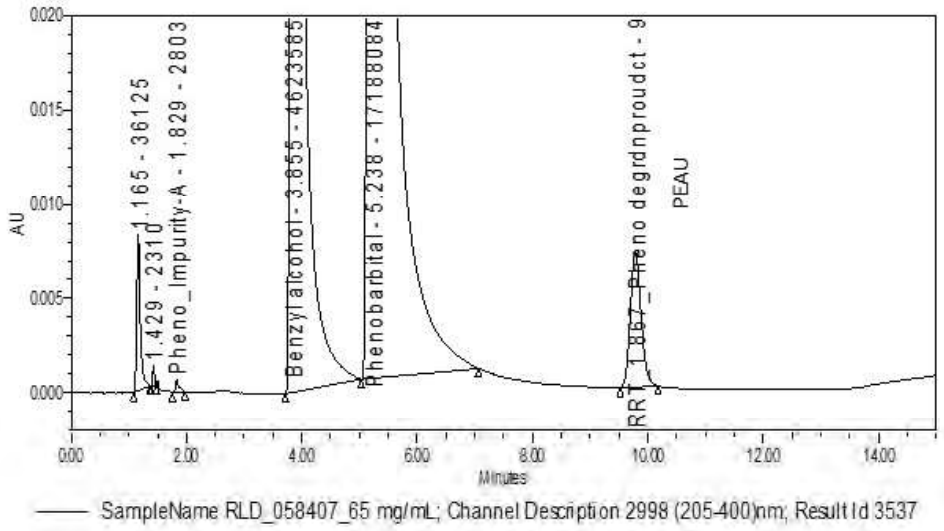
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627538	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

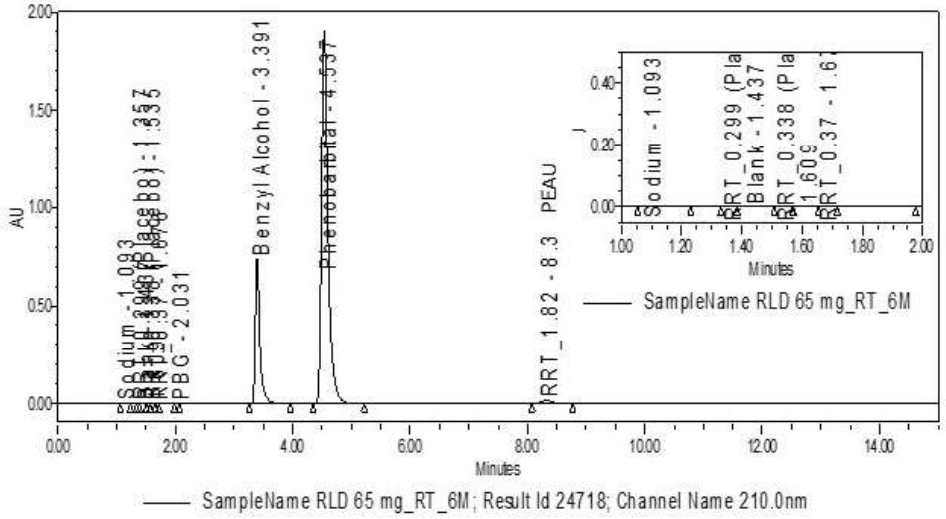
Fig. 3D



SampleName RLD_058407_65 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3537

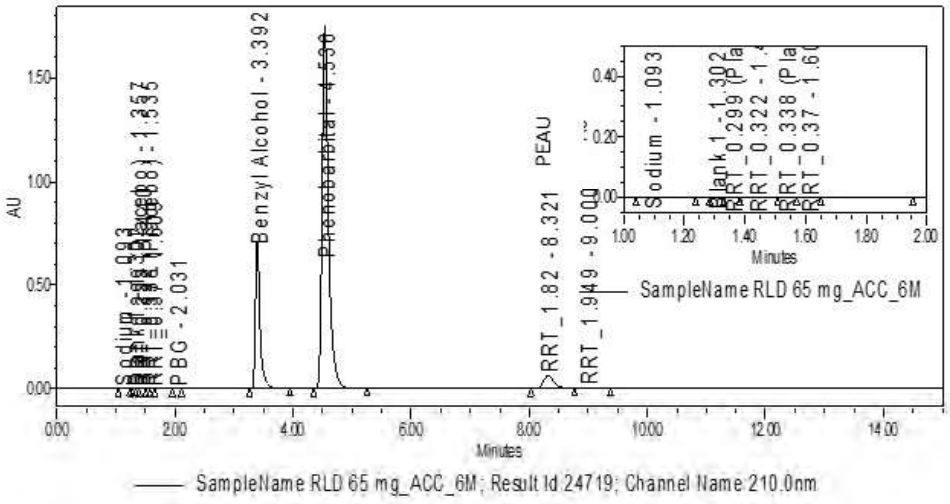
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.07	17.1	390.1	12312.8	1.5
2	Pheno_Impurity-A	1.829	2803	0.01	5.2	0.3	7608.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1018.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92937	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



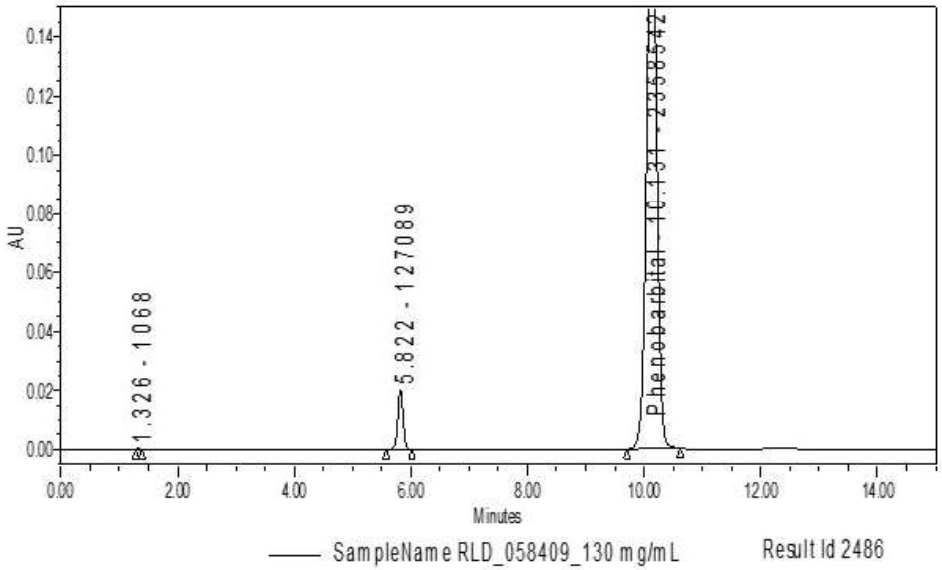
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



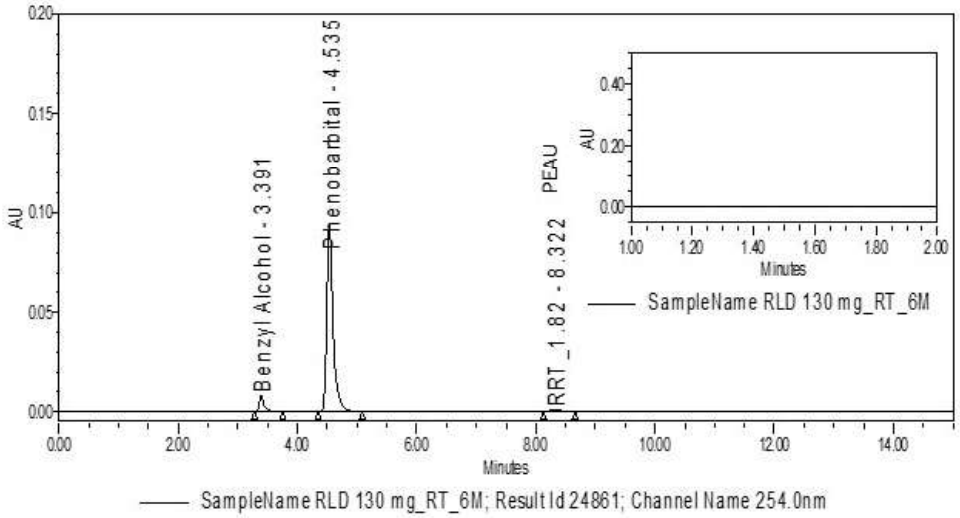
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



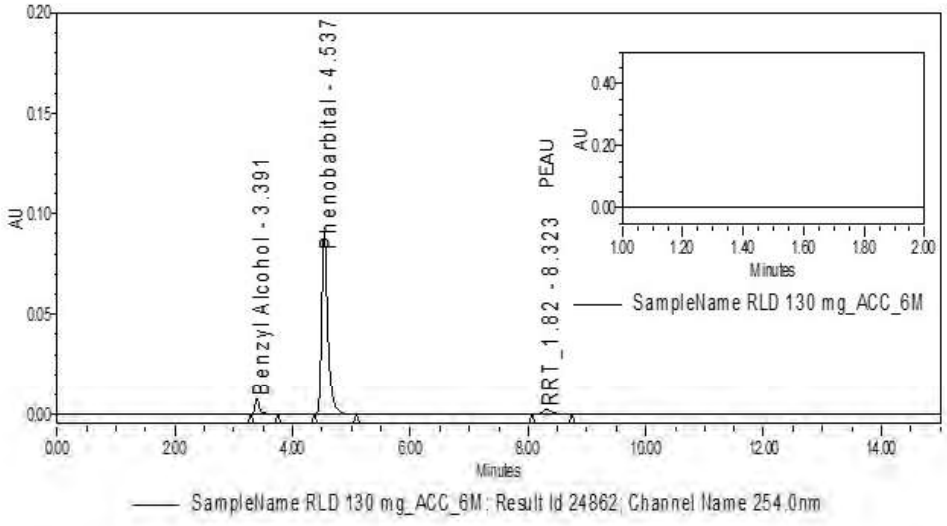
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



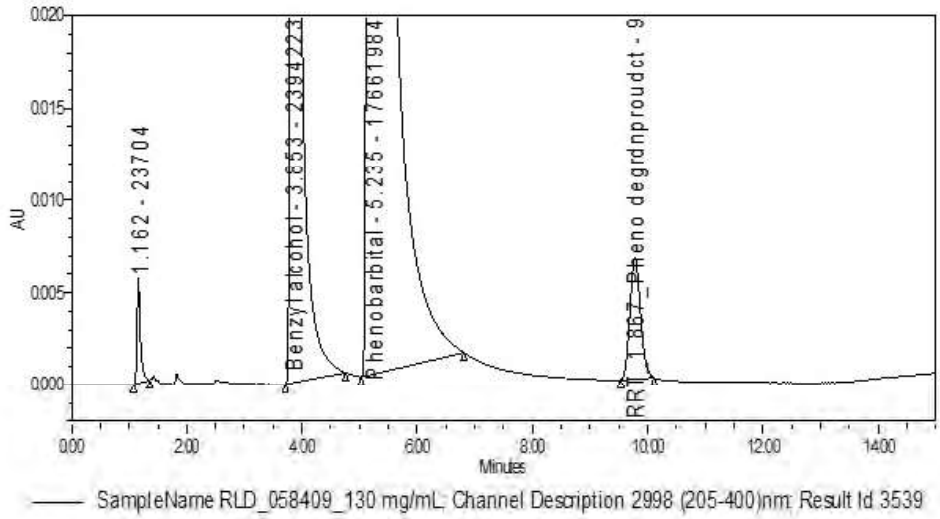
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



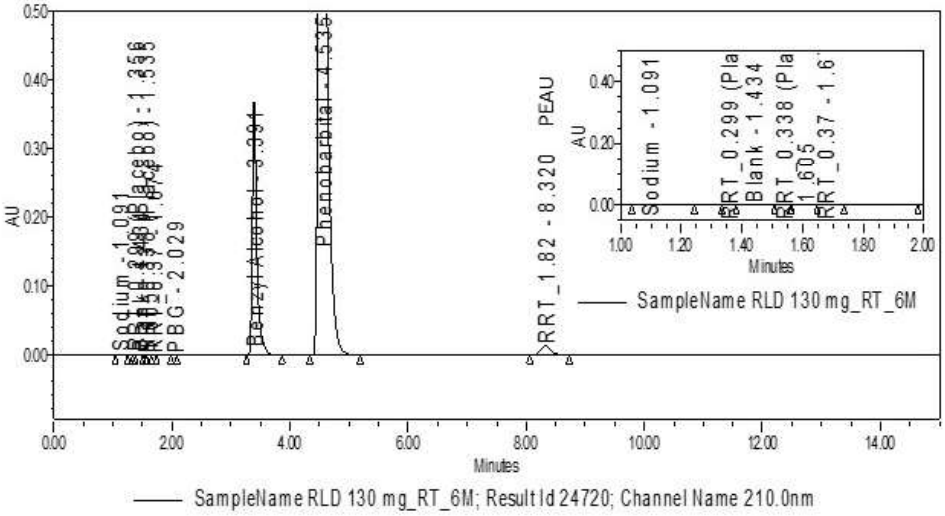
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



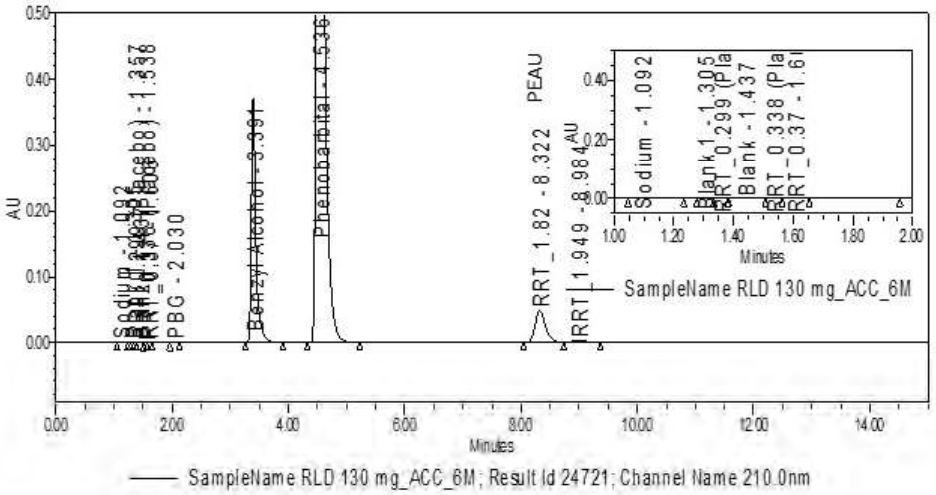
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3853	2394223	11.87	20.8	223.9	12438.0	1.5
2	Phenobarbital	5.235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Pheno degrdnproudct	9.776	83640	0.41	16.6	3.5	13612.7	1.1

Fig. 3K



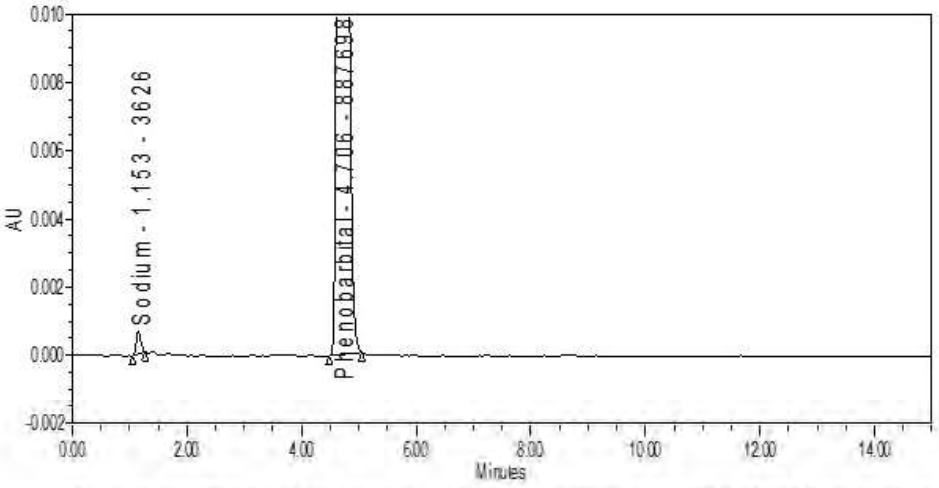
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

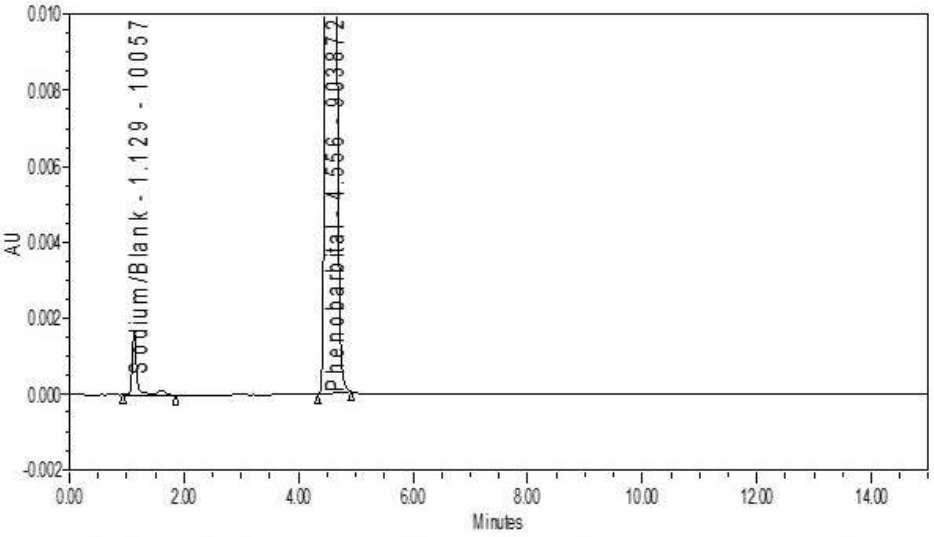
Fig. 4A



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887698	58.858	mg/mL	99.1	19.3	52343.5	7952.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

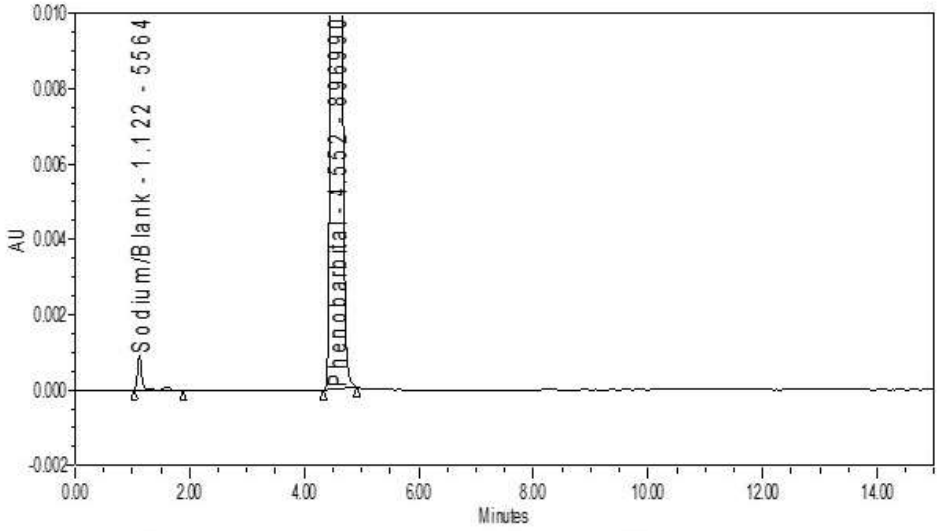
Fig. 4B



SampleName NPH1907_65mg_RT_6M; Channel Description W2489 ChB 254nm; Result Id 31317

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.388	mg/mL	100.0	20.8	44822.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

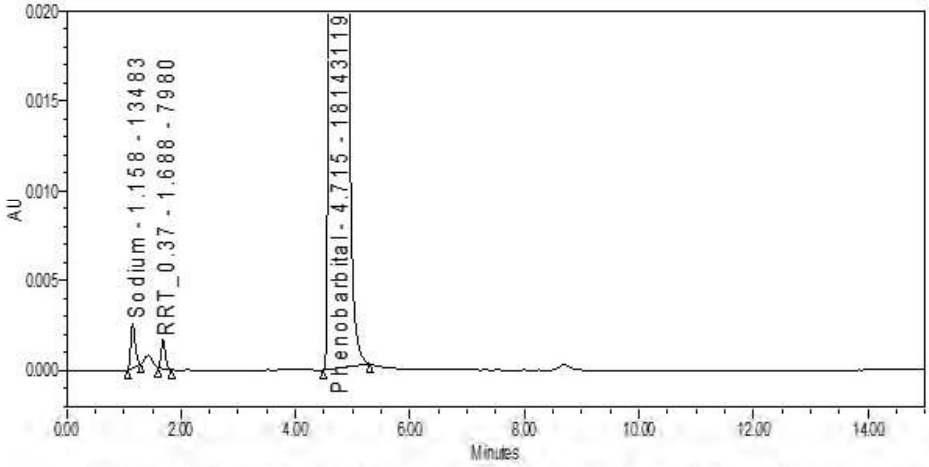
Fig. 4C



SampleName NPH1907_65mg_ACC_6M; Channel Description W2489 ChB 254nm; Result Id 31320

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	896990	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1275.7	1.3

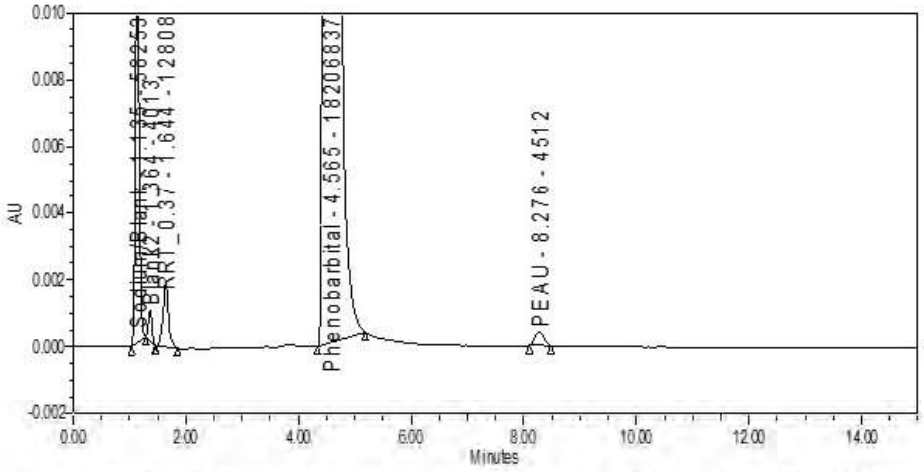
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

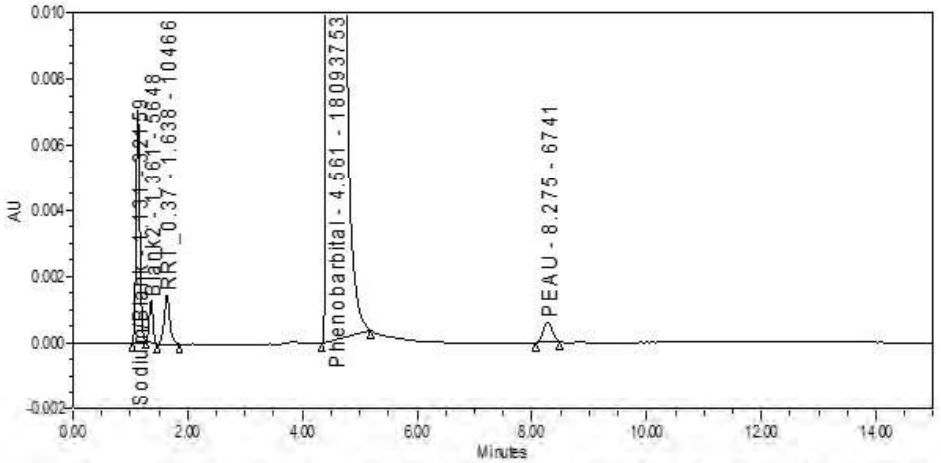
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.88	58.872	mg/mL	17.3	10731013	7604.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.026	mg/mL	3.7	772.4	2602.6	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1039.2	1.2

Fig. 4E



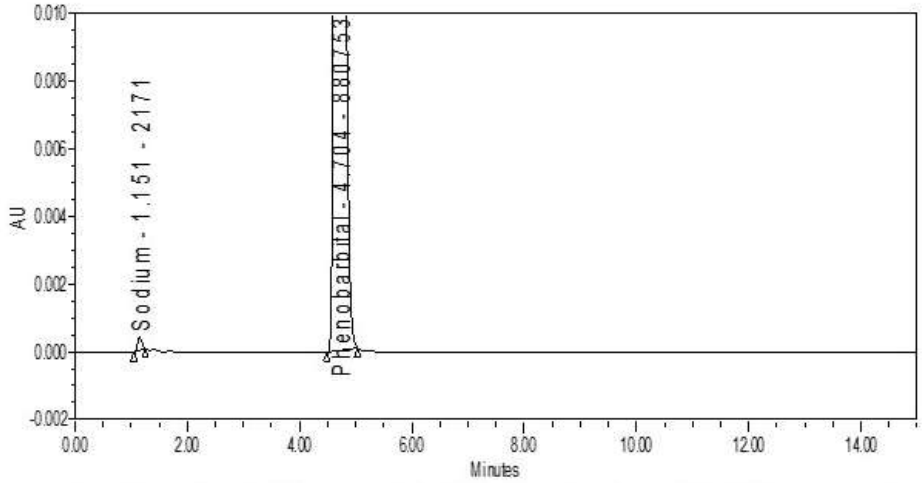
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4013	0.02			1.9	626.1	22417	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12239.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	1616675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	Sodium/Blank	1.135	58253	0.32	0.173	mg/mL		8406.1	1363.0	1.1

Fig. 4F



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	5648	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11918.8	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1693108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1064.2	1482.5	1.1
5	Sodium/Blank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

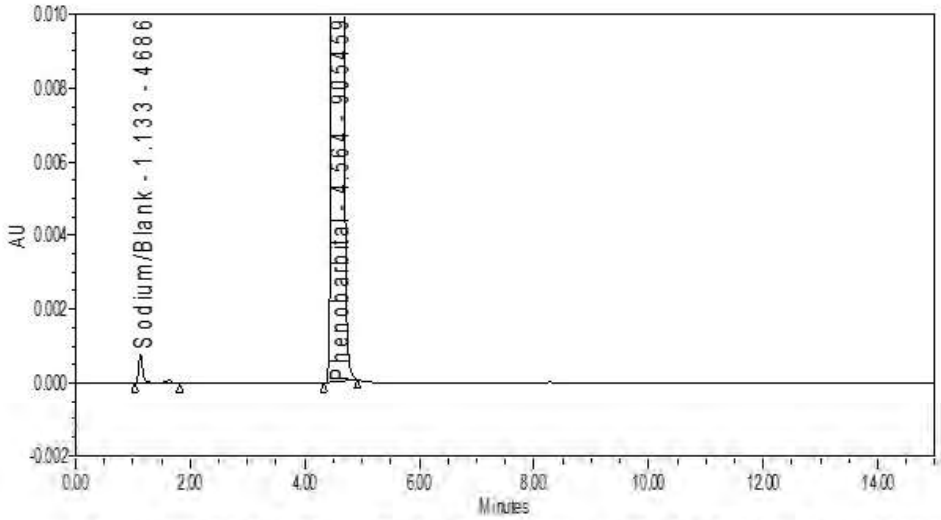
Fig. 4G



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

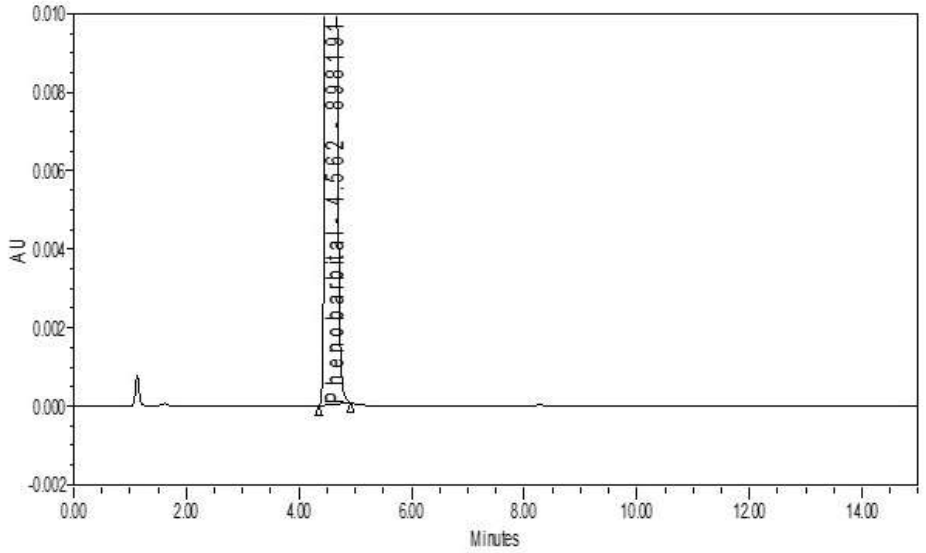
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	880753	116.796	mg/mL	98.3	19.3	40192.1	7866.8	1.2
2	Sodium	1.151	2171					148.3	959.0	1.0

Fig. 4H



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	55858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

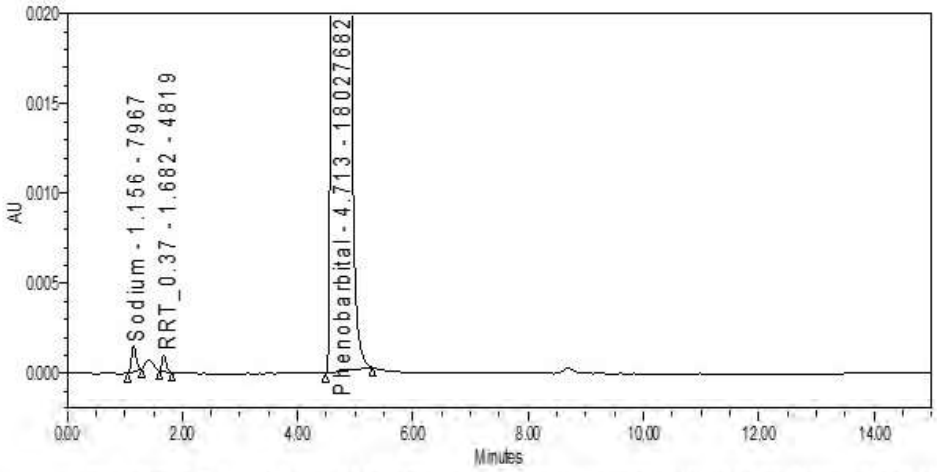
Fig. 4I



—— SampleName NPH1912_130mg_ACC_6M ; Channel Description W2489 ChB 254nm; Result Id 31328

	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898191	118.030	mg/mL	99.4	55375.6	8693.8	1.1

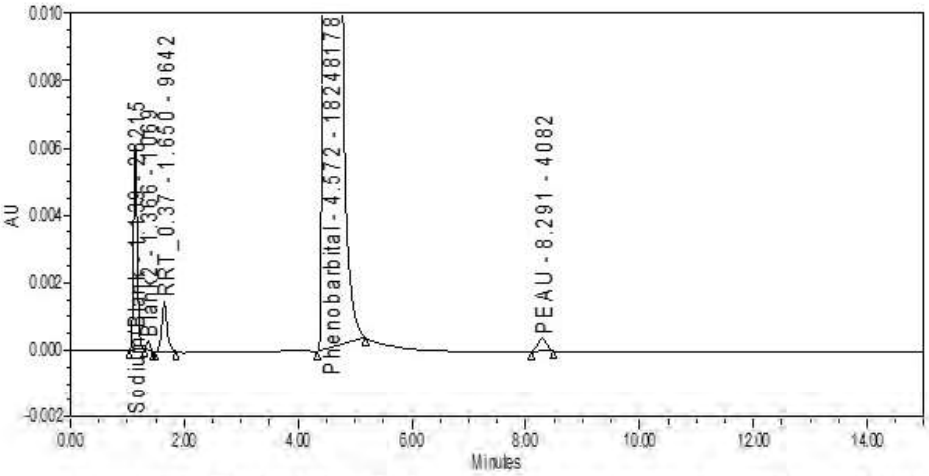
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14048

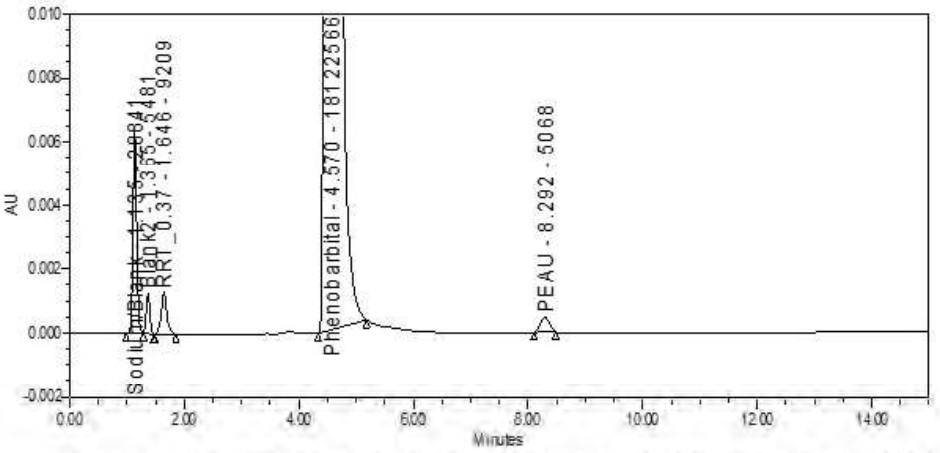
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.0	1001026.6	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	433.7	2401.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

Fig. 4K



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.8	1.0
3	Phenobarbital	4.572	18248178	99.76	108.187	mg/mL	15.9	1373502.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	2.0	832.7	1618.4	1.1
5	Sodium/Blank	1.139	28215	0.15	0.167	mg/mL		3438.2	1382.8	1.1

Fig. 4L



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChA 210nm; Result Id 31640

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.365	5481	0.03			1.9	687.2	2149.1	1.1
2	PEAU	8.292	5068	0.03	0.030	mg/mL	14.8	256.0	12320.6	1.0
3	Phenobarbital	4.570	18122566	99.73	107.442	mg/mL	15.1	1320858.2	8330.4	1.1
4	RRT_0.37	1.646	9209	0.05	0.055	mg/mL	1.8	725.3	1481.0	1.1
5	Sodium/Blank	1.135	28841	0.16	0.171	mg/mL		3440.5	1392.6	1.1

Fig. 5A

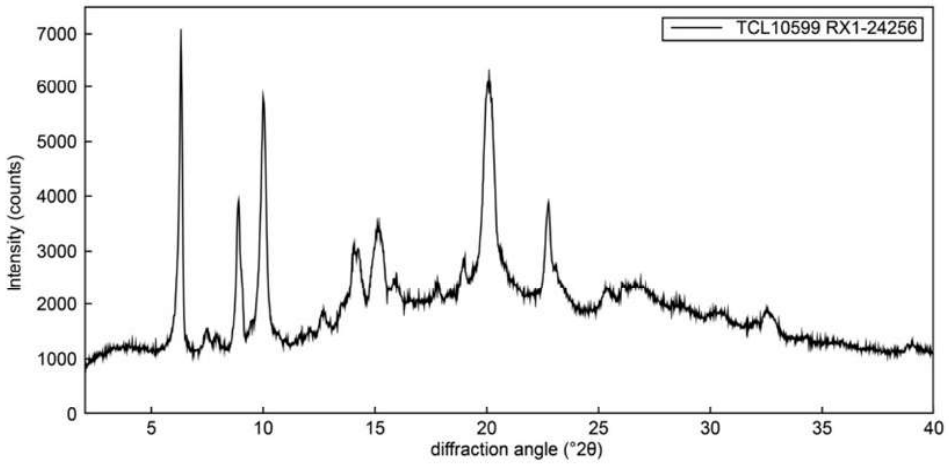

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Intensity (counts)
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5000
4000
3000
2000
1000
0
5
10
15
20
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30
35
40
diffraction angle (°2θ)

Fig. 5B

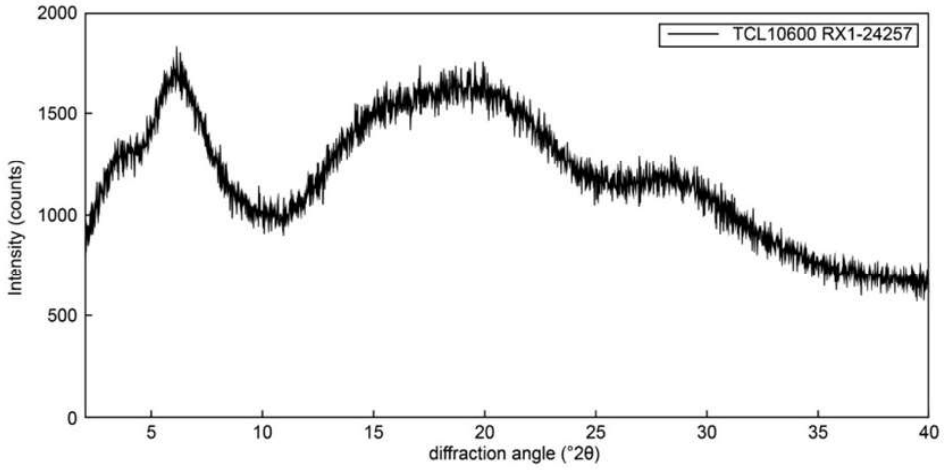

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Intensity (counts)
diffraction angle (°2θ)
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5
10
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20
25
30
35
40

Fig. 5C

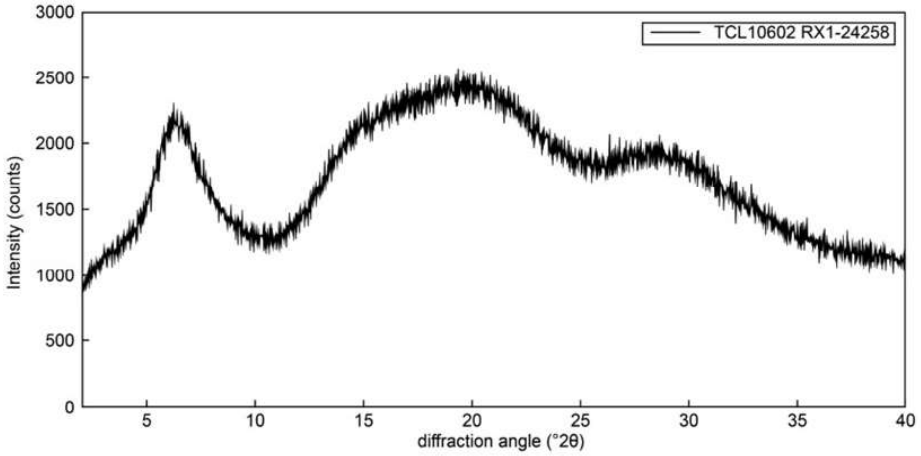
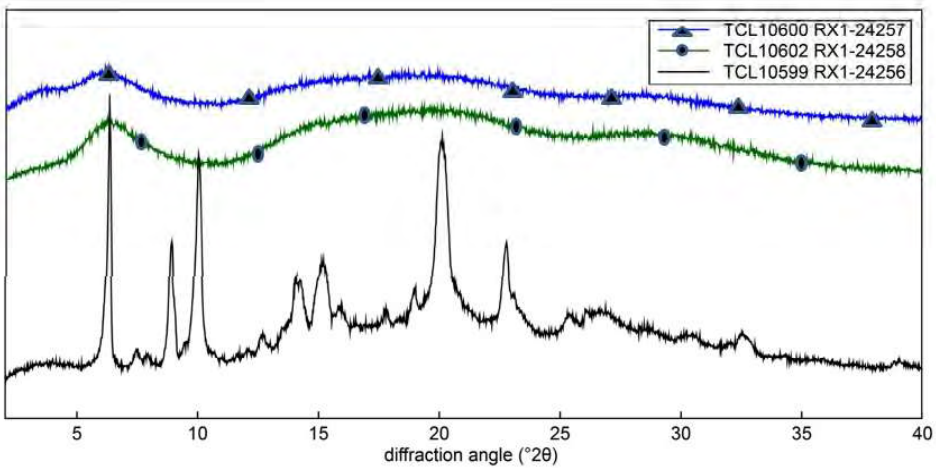

TCL10602 RX1-24258
Intensity (counts)
diffraction angle (°2θ)
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1000
1500
2000
2500
3000
5
10
15
20
25
30
35
40

Fig. 5D


TCL10600 RX1-24257
TCL10602 RX1-24258
TCL10599 RX1-24256
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Anand Shukla Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Bala Tripura Sundari Chodavarapu Date (Optional): _____

Signature: Bala Tripura Sundari Chodavarapu

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Jay Shukla Date (Optional): _____

Signature: Jay Shukla

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Dasaradhi Lakkaraju Date (Optional) : _____

Signature: Dasaradhi Lakkaraju

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Thirupathi Mangali Date (Optional): _____

Signature: Thirupathi Mangali

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:	LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT			
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu			
Filer:	Martin Fessenmaier/Danielle Moroz			
Attorney Docket Number:	104078.0001US3			
Filed as Small Entity				
Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	64	64
UTILITY SEARCH FEE	2111	1	280	280
UTILITY EXAMINATION FEE	2311	1	320	320
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	1680	1680
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	56	56
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2400**

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18100804 Document Date: 01/24/2023

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

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- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

File History Content Report

The following content is missing from the original file history record obtained from the United States Patent and Trademark Office. No additional information is available.

Document Date - 2023-01-24

Document Title - Applicant Communication Re: Entity Status Set to Undiscounted (Initial Default Setting or Status Change)

This page is not part of the officia2 USPTO record. It has been determined that content identified on this document is missing from the original file history record.

File History Content Report

The following content is missing from the original file history record obtained from the United States Patent and Trademark Office. No additional information is available.

Document Date - 2023-02-14

Document Title - Applicant Communication Re: Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27

This page is not part of the official USPTO record. It has been determined that content identified on this document is missing from the original file history record.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/100,804	01/24/2023		664	104078.0001US3	20	1

CONFIRMATION NO. 9426

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

FILING RECEIPT

OC000000053795791

Date Mailed: 02/17/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Bala Tripura Sundari Chodavarapu, Davis, CA;
Thirupathi Mangali, Sacramento, CA;
Jay Shukla, Sacramento, CA;
Anand Shukla, Denver, CO;
Dasaradhi Lakkaraju, Sacramento, CA;

Applicant(s)

Nivagen Pharmaceuticals, Inc., Sacramento, CA;

Assignment For Published Patent Application

Nivagen Pharmaceuticals, Inc., Sacramento, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/854,914 06/30/2022
which is a CIP of 17/025,881 09/18/2020 PAT 11,406,598
which claims benefit of 62/903,511 09/20/2019

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 02/14/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/100,804**

Projected Publication Date: 05/25/2023

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Lyophilized Compositions of Phenobarbital Sodium Salt

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 03/15/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
03/15/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/100,804	**Applicant(s)** Chodavarapu et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 24 January 2023 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

Electronic Acknowledgement Receipt	
EFS ID:	47882271
Application Number:	18100804
International Application Number:	
Confirmation Number:	9426
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	104078.0001US3
Receipt Date:	21-APR-2023
Filing Date:	24-JAN-2023
Time Stamp:	13:17:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDS-01.pdf	1283670 5a2d5a5020a162082129830146316c889b3dcb85	no	5

Warnings:

Information:	
Total Files Size (in bytes):	1283670

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18100804
	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	
	Attorney Docket Number	104078.0001US3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Martin Fessenmaier/	Date (YYYY-MM-DD)	2023-04-21
Name/Print	Martin Fessenmaier	Registration Number	46697

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	18100804
Filing Date	2023-01-24
First Named Inventor	Bala Tripura Sundari Chodavarapu
Art Unit	1615
Examiner Name	
Attorney Docket Number	104078.0001US3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6077545	A	2000-06-20	Roskos et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20100035904	A1	2010-02-11	Sun et al.	
	2	20170143719	A1	2017-05-25	Parker et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	104940149	CN	A	2015-09-30	Sun		
	2	2017085687	WO	A1	2017-05-26	WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED		

EFS Web 2.1.18

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18100804
	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	
	Attorney Docket Number	104078.0001US3

If you wish to add additional Foreign Patent Document citation information please click the Add button [Add]

NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	BARDAT et al., "Moisture Measurement: A New Method for Monitoring Freeze-drying Cycles," Journal of Parenteral Science & Technology, 1993 November-December; 47(6):293-299.	
	2	DIETZ et al., "Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs," Pharmaceutical Research, 1988; 5(12):803-805.	
	3	FDA, "Lyophilization of Parenteral: Guide to Inspections of Lyophilization of Parenterals," published 2014-11-11; 22 pgs.	
	4	GUPTA, V. Das, "Effect of Ethanol, Glycerol, and Propylene Glycol on the Stability of Phenobarbital Sodium," Journal of Pharmaceutical Sciences, 1984 November 1; 73(11):1661-1662. Abstract only.	
	5	JATUL, Bernard B., "The Stability of Solutions of Phenobarbital Sodium," A Dissertation Presented to the Graduate Council of the University of Florida, 1943 February; 170 pgs.	
	6	KELLY et al., "Phenobarbital Sodium," London Health Sciences Centre; Last Update: 2018 October 11; 4 pgs. Retrieved from the internet on 2020 November 18: https://www.lhsc.on.ca/critical-care-trauma-centre/phenobarbital-sodium.	
	7	NAHATA et al., "Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection," American Journal of Hospital Pharmacy, 1986 February; 43:384-385.	
	8	NAYYAR et al., "Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients?" Journal of Applied Pharmaceutical Science, 2012; 02(06):230-235.	
	9	SNYDER, Meg, "Lyophilization: The Basics - Drug Discovery and Development," 2017 March 7; pgs. 1-5. Retrieved from the internet on 2020 November 19: https://www.drugdiscoverytrends.com/lyophilization-the-basics/#:~:text=Some of the advantages of,to heat the product excessively.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18100804
	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	
	Attorney Docket Number	104078.0001US3

	10	STAUDT, "Phenobarbital in newborn infants: Overview," Monatsschr Kinderheilkd, 1984 April; 132(4):194-202. Abstract only.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Other Prior Art

According to the information contained in form PTO-1449 or PTO-892, there are one or more other prior art/non-patent literature documents missing from the original file history record obtained from the United States Patent and Trademark Office. Upon your request we will attempt to obtain these documents from alternative resources. Please note that additional charges will apply for this service.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3

CONFIRMATION NO. 9426

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

PUBLICATION NOTICE



Date Mailed: 05/25/2023

Title: Lyophilized Compositions of Phenobarbital Sodium Salt
Publication No.US-2023-0157959-A1
Publication Date:05/25/2023

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211,et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to the applicant. A copy of the publication may be obtained from the Office upon payment of the application fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571)272-3150 or (800)972-6382, by facsimile at (571)273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic business center at www.upsto.gov using the public side of the Patent Application Information and Retrieval(PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Furhter assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000 or (571) 272-4200 or 1-888-786-0101

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 06/23/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
06/23/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 18/100,804	Applicant(s) Chodavarapu et al.	
	Examiner CARLOS A AZPURU	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 01/24/2023 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 04212023.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A Track One request was granted on 03/15/2023.

Information Disclosure Statement

An information disclosure statement was filed on 04/21/2023.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support could be found for the drying step without the use of a vacuum. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 1-20 is/are rejected under 35 U.S.C. 103 as being unpatentable over US 200/0215750 (Parker) in view of FDA_7/93 (11/11/2014).

Parker teach a storage stable phenobarbital sodium solution for injection with a concentration in an amount between 15 and 200 mg/mL, and a pH between 9 and 12 (Abstract). Parker also teaches that the solutions are extremely stable, and do not generate any significant amounts o impurities, including phenyl ethyl acetyl urea (PEAU) and phenyl butyric acid (PBA) during extended storage ([0016] – [0017]). Parker does not lyophilize its product.

FDA_7/93 is directed to Lyophilization of Parental teaches that the lyophilization process consists of separate, unique, and interdependent processes freezing, primary drying (sublimation), and secondary drying (1st para of page 1/22 which reads on the process of removing water in the instant claim 1)). FDA_7/93 teaches the following steps: Dissolving, Sterilizing, Filling into individual sterile containers, transporting the stoppered containers into a chamber under aseptic conditions, feezing the solution, applying a vacuum chamber and heating the shelves in the water from the frozen state, then complete stoppering of the vials.

FDA_7/93 indicates that products are manufactured in the lyophilized from due to their instability when in solution (2nd paragraph, Product Type/Formulation, page 2/22)). The free water in a product is that water that is absorbed on the surfaces of the product and must be removed to limit

further biological and chemical reactions (4th and 6th paragraph, page 16/22). FDA_7/93 further teaches that an obvious concern with the lyophilized product is the amount of moisture present in vials. Moisture specifications for both product release and stability are discussed. Stability testing includes provisions for the assay of aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labelling (see 1st and 4th paragraphs under Stability Testing on page 13/22. Additionally, FDA_7/93 teaches that the product is frozen at a temperature well below the eutectic point. It is desirable after freezing and during primary drying to hold the drying temperature of the product at least 4-50 degrees below the eutectic point.

Therefore, it would have been well within the skill of the ordinary practitioner to claim the stable product as taught by Parker, and further, to include the water content, humidity, and temperatures of the instant claims as part of the lyophilization product as taught by FDA_7/93, with a reasonable expectation of similar shelf stability. The instant claims would have been obvious to one of ordinary skill in the art at the time of filing over Parker in view of FDA_7/93.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARLOS A AZPURU whose telephone number is (571)272-0588. The examiner can normally be reached 9 am- 3 pm, 4 pm-8pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617
caz

Notice of References Cited	Application/Control No. 18/100,804	Applicant(s)/Patent Under Reexamination Chodavarapu et al.	
	Examiner CARLOS A AZPURU	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20170143719-A1	05-2017	Parker; Michael G.	A61K31/515	1/1
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	FDA, " Lyophilization of Parental Guide to Inspection of Lyophilized Parentals", pages 1-22. (Year: 2014)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Other Prior Art

According to the information contained in form PTO-1449 or PTO-892, there are one or more other prior art/non-patent literature documents missing from the original file history record obtained from the United States Patent and Trademark Office. Upon your request we will attempt to obtain these documents from alternative resources. Please note that additional charges will apply for this service.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18100804
	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	
	Attorney Docket Number	104078.0001US3

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Martin Fessenmaier/	Date (YYYY-MM-DD)	2023-04-21
Name/Print	Martin Fessenmaier	Registration Number	46697

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	18100804
Filing Date	2023-01-24
First Named Inventor	Bala Tripura Sundari Chodavarapu
Art Unit	1615
Examiner Name	Carlos A Azpuru
Attorney Docket Number	104078.0001US3

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/C.A.A/	1	6077545	A	2000-06-20	Roskos et al.	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/C.A.A/	1	20100035904	A1	2010-02-11	Sun et al.	
/C.A.A/	2	20170143719	A1	2017-05-25	Parker et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/C.A.A/	1	104940149	CN	A	2015-09-30	Sun		
/C.A.A/	2	2017085687	WO	A1	2017-05-26	WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18100804
	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	Carlos A Azpuru
	Attorney Docket Number	104078.0001US3

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NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
/C.A.A/	1	BARDAT et al., "Moisture Measurement: A New Method for Monitoring Freeze-drying Cycles," Journal of Parenteral Science & Technology, 1993 November-December; 47(6):293-299.	
/C.A.A/	2	DIETZ et al., "Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs," Pharmaceutical Research, 1988; 5(12):803-805.	
/C.A.A/	3	FDA, "Lyophilization of Parenteral: Guide to Inspections of Lyophilization of Parenterals," published 2014-11-11; 22 pgs.	
/C.A.A/	4	GUPTA, V. Das, "Effect of Ethanol, Glycerol, and Propylene Glycol on the Stability of Phenobarbital Sodium," Journal of Pharmaceutical Sciences, 1984 November 1; 73(11):1661-1662. Abstract only.	
/C.A.A/	5	JATUL, Bernard B., "The Stability of Solutions of Phenobarbital Sodium," A Dissertation Presented to the Graduate Council of the University of Florida, 1943 February; 170 pgs.	
/C.A.A/	6	KELLY et al., "Phenobarbital Sodium," London Health Sciences Centre; Last Update: 2018 October 11; 4 pgs. Retrieved from the internet on 2020 November 18: https://www.lhsc.on.ca/critical-care-trauma-centre/phenobarbital-sodium.	
/C.A.A/	7	NAHATA et al., "Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection," American Journal of Hospital Pharmacy, 1986 February; 43:384-385.	
/C.A.A/	8	NAYYAR et al., "Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients?" Journal of Applied Pharmaceutical Science, 2012; 02(06):230-235.	
/C.A.A/	9	SNYDER, Meg, "Lyophilization: The Basics - Drug Discovery and Development," 2017 March 7; pgs. 1-5. Retrieved from the internet on 2020 November 19: https://www.drugdiscoverytrends.com/lyophilization-the-basics/#:~:text=Some of the advantages of,to heat the product excessively.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2023-01-24
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1615
	Examiner Name	Carlos A Azpuru
	Attorney Docket Number	104078.0001US3

/C.A.A/	10	STAUDT, "Phenobarbital in newborn infants: Overview," Monatsschr Kinderheilkd, 1984 April; 132(4):194-202. Abstract only.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/CARLOS A AZPURU/	Date Considered	06/16/2023

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Sep 7 2023

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Martin Fessenmaier

S-signature:
/Martin Fessenmaier/

Registration Number:
46697

U.S. Application Number:
18100804

Confirmation Number:
9426

E-mail Address:
mfessenmaier@umbergzipser.com

Phone Number:
+1 9497359158

Proposed Time of Interview:
9-20-2023 2:00 PM ET

Alternative Proposed Time(s) of Interview:
9-20-2023 3:00 PM ET

Alternative Proposed Time(s) of Interview:
9-20-2023 2:00 PM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:
Draft amendments for response to NFOA

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/100,804	**09/20/2023 02:59:48 PM ET**	**104078.0001US3**

Title of Invention

Lyophilized Compositions of Phenobarbital Sodium Salt

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9426	FILED BY	Danielle Moroz
PATENT CENTER #	62832943	FILING DATE	01/24/2023
CUSTOMER #	149344	FIRST NAMED INVENTOR	Bala Tripura Sundari Chodavarapu
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Martin Fessenmaier

Documents **TOTAL DOCUMENTS: 4**

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Response-01_to_NFOA_dated_06-23-2023_REV004.pdf		9	-	172 KB
Response-01_to_NFOA_dated_06-23-2023_REV004-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	115 KB
Response-01_to_NFOA_dated_06-23-2023_REV004-CLM.pdf	(2-4)	3	Claims	96 KB
Response-01_to_NFOA_dated_06-23-2023_REV004-REM.pdf	(5-8)	4	Applicant Arguments/Remarks Made in an Amendment	129 KB

Response-01_to_NFOA_dated_06-23-2023_REV004-INTRVIEW.APP.pdf	(9-9)	1	Applicant summary of interview with examiner	93 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Response-01_to_NFOA_dated_06-23-2023_REV004.pdf	BF1ED70009A9B199E2BC7F49B3923D65BE1A75DC8DE6842D411416C4291D8202AE04DB421B35E5B692797AD41C7D9FCE9E48498057FE4D18C1AFFFF5E45E3F2D
Response-01_to_NFOA_dated_06-23-2023_REV004-A....pdf	77FF12713D6C04C1EAB00E48DD76650B3D5F254233B7C096600AF3C64B6BF8117FD34EF3C6B5B374781CD908C369F159AD2DAE7FE02A01048DDE5FEDD6B02EB3
Response-01_to_NFOA_dated_06-23-2023_REV004-CLM.pdf	80BFE020FCB9ADF7CAD2D2430A230790063D8FA0EEF3CF8CB45B579A48E6E3C78AE13427A08F86CD7EA491F66C76EED3961346EEB91037101430E6068B9677B8
Response-01_to_NFOA_dated_06-23-2023_REV004-REM.pdf	8C16D46F169ED2581B704209548B99F81E9EACF6F95B4C46D3664A910D04A3A7620C34F931244A366B1D7AAA2049DD407BAADCC1FD054B2ADA83BCC7B6C6C6E3
Response-01_to_NFOA_dated_06-23-2023_REV004-INTRVIEW.APP.pdf	B483593905A2E08623BDBCA20986337C6AFCA7D41ED9F56D65FA9927B997A2720A2B7B5BB2846CA9641E59E4E7230A2696604EF2030CE7D6FC9138CA3370589A

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C.

371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl No.:	18/100,804	Examiner:	Carlos A AZPURU
First Inventor:	Bala Tripura Sundari Chodavarapu	Art Unit:	1617
Filing Date:	2023-01-24	Docket No.:	104078.0001US3
Title	Lyophilized Compositions of Phenobarbital Sodium Salt		

RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This paper responds to the Office Action dated 06/23/2023. Please enter the amendments shown herein.

- Claim amendments begin on page 2.
- Remarks begin on page 5.
- An Interview Summary is attached to this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims represents the current version of claims before the Office:

1-20. (canceled)

21. (new) A storage stable pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized, and

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

22. (new) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at 40°C for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

23. (new) The pharmaceutical product of claim 21, 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.

24. (new) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at 40°C for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

25. (new) The pharmaceutical product of claim 21, wherein the composition is amorphous.

26. (new) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at room temperature for 24 months and then reconstituted for

injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).

27. (new) A pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized,

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

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

28. (new) The pharmaceutical product of claim 27, 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.

29. (new) The pharmaceutical product of claim 27, 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).

30. (new) The pharmaceutical product of claim 27, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

31. (new) The pharmaceutical product of claim 30, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for

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

32. (new) The pharmaceutical product of claim 33, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

33. (new) The pharmaceutical product of claim 27, wherein the composition is amorphous.

REMARKS/ARGUMENTS

The Office Action dated 06/23/2023 has been received and carefully considered. By this amendment, previously pending claims 1-20 are canceled without prejudice to the claimed subject matter and new claims 21-33 are added. New claims 21-33 are fully supported by the specification of the present application and parent application US 17/025,881. After entry of this Amendment, claims 21-33 will be pending. With these amendments, no new matter is added. In view of these amendments and the following remarks, Applicants respectfully request reconsideration.

35 U.S.C. §112(a)

The Office rejected **claim 19** under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-Al A), first paragraph, as failing to comply with the written description requirement. More specifically, the Examiner noted that no support could be found for the drying step without the use of a vacuum.

As claim 19 is canceled and new claims 21-33 do not recite a drying step without the use of a vacuum, the rejection should be moot.

35 U.S.C. §103

The Office further rejected **claims 1-20** under 35 U.S.C. 103 as being unpatentable over US 200/0215750 (Parker) [*sic*] in view of FDA_7/93 (11/11/2014). As PTO-892 identifies Parker as US-20170143719-A1 and as that '719 reference teaches stable formulations of phenobarbital sodium injections, Applicant believes that the Office's rejection was intended to be based on the '719 reference.

As original claims 1-20 were canceled, the rejection should be moot.

Regarding new claims 21-33 in view of Parker and FDA_7/93, Applicant agrees with the Office that Parker is concerned with stability of phenobarbital sodium in an injectable solution containing the phenobarbital sodium and that Parker does not lyophilize its product. Applicant also agrees with the Office's general characterization of certain aspects of lyophilization in FDA_7/93.

However, Applicant respectfully disagrees for various reasons with the Office's argument that "...it would have been well within the skill of the ordinary practitioner to claim the stable

product as taught by Parker, and further, to include the water content, humidity, and temperatures of the instant claims as part of the lyophilization product as taught by FDA_7/93, with a reasonable expectation of similar shelf stability..."

First, Applicant notes that the demonstrated stability of phenobarbital sodium in Parker's injectable solution would not motivate a skilled artisan to further modify Parker's formulation as the problem of stability of phenobarbital sodium was already solved. As such, *Parker does not provide a motivation to modify* his formulation in a manner such as to arrive at the present claims and therefore lacks an essential requirement to properly establish obviousness[1].

Second, Parker uses in his formulations a number of stabilizing co-solvents such as glycols (*e.g.*, propylene glycol) and C_1-C_4 alcohols (*e.g.*, ethanol) in quantities that exceed the amount of phenobarbital sodium. With respect to glycols, it must be appreciated that glycols are not volatile under lyophilization conditions and will therefore remain in the lyophilization vial together with the phenobarbital sodium. Therefore, lyophilization of the composition of Parker *will not produce a composition* that "comprises no less than 98% phenobarbital sodium" *as presently claimed*.

Third, and notwithstanding the above noted arguments, Applicant notes that while the term 'lyophilization' in general describes a process of water removal by sublimation, there is a wide range of lyophilization processes and lyophilization conditions (*e.g.*, temperature, pressure, time at the temperature and/or pressure for each of the freezing, primary and secondary drying steps) that will lead to a wide range of physicochemical parameters of the lyophilized product. Indeed, FDA_7/93 cited by the Examiner expressly states that "...Studies have shown the rate and manner of freezing may affect the quality of the lyophilized product (page 6/22, lines 9-10, 13-14)...". As such, even if one would have hypothetically considered lyophilizing Parker's formulation, FDA_7/93 fails to provide any guidance as to what lyophilization processes and lyophilization

[1] See KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 407 (2007); In re Dembiczak, 175 F.3d 994, 998–99 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." (citations omitted)); ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577 (Fed. Cir. 1984) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so.").

conditions should be chosen to arrive at the lyophilized product as presently claimed. Viewed from a different perspective, neither Parker nor FDA_7/93 provide a reasonable expectation of success for a lyophilized product as presently claimed. In addition, and with further respect to dependent claims 25 and 33, the skilled artisan would not have reasonably expected the lyophilized product to be amorphous. In particular, and as noted in Applicant's specification, the claimed stability is particularly surprising and unexpected in view of the fact that conventional wisdom teaches that *crystalline material is more stable than amorphous material* (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). In that context, storage stability (chemically stable during storage, and upon reconstitution in water, will not form significant amounts of the toxic degradation products (esp. PEAU, 2EPMM, or PBG)) is particularly desirable as commonly observed toxic byproducts caused severe side effects, particularly in neonates.

For at least the above arguments, it is the Applicant's position that claims 21-37 are not obvious over Parker in view of FDA_7/93. Applicant respectfully requests reconsideration and that a notice of allowance be issued in due course.

///

Request For Allowance

Claims 21-33 are pending in this application. Applicant requests allowance of all pending claims.

Respectfully submitted,
Umberg Zipser LLP

Date: September 20, 2023

By: /Martin Fessenmaier Ph.D./
Martin Fessenmaier Ph.D.
Reg. No. 46697

Umberg Zipser LLP
1920 Main Street, Suite 750
Irvine, CA 92614
Telephone (949) 679-0052
Fax (949) 679-0461

INTERVIEW SUMMARY

Sir:

In response to the telephonic interview conducted on September 20, 2023, Applicant submits the interview summary in accordance to MPEP 713:

(A) Application number: 18/100,804

(B) Name of applicant: Nivagen Pharmaceuticals, Inc.

(C) Name of examiner: CARLOS A AZPURU

(D) Date of interview: September 20, 2023.

(E) Type of interview: The interview was conducted by telephone.

(F) Name of participant(s) (applicant, applicant's representative, etc.): Applicant's agent was Martin Fessenmaier (Patent Agent; Reg.No.46697) and Applicant's representative was Paul Rauch.

(G) An indication whether or not an exhibit was shown or a demonstration conducted: -/-

(H) An identification of the claims discussed: Proposed new claims 21-33.

(I) An identification of the specific prior art discussed: Parker and FDA, of record.

(J) An indication whether an agreement was reached and if so, a description of the general nature of the agreement: The applicant discussed the distinction between the art of record and the proposed new claims, and it was agreed that the proposed new claims distinguish over the cited art.

Respectfully submitted,
Umberg/Zipser, LLP

Date: _September 20, 2023_____

By _/Martin Fessenmaier/_____
Martin Fessenmaier, Ph.D.
Reg. No. 46697

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Irvine, CA 92614
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 09/25/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/25/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	Application No. 18/100,804	Applicant(s) Chodavarapu et al.		
	Examiner CARLOS A AZPURU	Art Unit 1617	AIA (First Inventor to File) Status Yes	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
CARLOS A AZPURU	Primary Examiner	Telephonic
Martin Fessenmaier	Attorney of Record	
Dr Rauch	Attorney	

Date of Interview: 20 September 2023

Issues Discussed:

35 U.S.C. 103

Mr Fessenmaier pointed out the fact that neither reference points to a concentration of no less than 98%, or the specific conditions necessary to obtain these results. New claims were proposed setting out these limitations. It was agreed that the references do no address this. A new search will be conducted on the amended claims, but the existing rejections appear to be overcome. If new rejections are found, a call will be placed to Mr Fessenmaier.

/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Transaction History Date 2023-10-16
Date information retrieved from USPTO Patent Application Information Retrieval (PAIR) system records at www.uspto.gov

Notice of Allowability	**Application No.** 18/100,804	**Applicant(s)** Chodavarapu et al.	
	Examiner CARLOS A AZPURU	**Art Unit** 1617	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment filed 09/20/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-33 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Withdrawn Rejection(s)

The rejections under 35 USC 112, first paragraph, or written description and 35 USC 103 are withdrawn in view of applicant's amendments and arguments filed 09/20/2023.

Allowable Subject Matter

Claims 21-33 are allowed.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: The prior art neither teaches, nor fairly suggests the claimed pharmaceutical. Specifically, neither the Parker reference, nor the FDA_7/93 reference teach the amount of phenobarbital, the reaction conditions to form it, or its amorphous property. The instant claims are allowable over the prior art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARLOS A AZPURU whose telephone number is (571)272-0588. The examiner can normally be reached 9 am- 3 pm, 4 pm-8pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617
caz

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NOTICE OF ALLOWANCE AND FEE(S) DUE

149344 7590 10/16/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/16/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

TITLE OF INVENTION: Lyophilized Compositions of Phenobarbital Sodium Salt

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	01/16/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

149344 7590 10/16/2023
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

TITLE OF INVENTION: Lyophilized Compositions of Phenobarbital Sodium Salt

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	01/16/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
AZPURU, CARLOS A	1617	424-489000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 10/16/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/16/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

BEST COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Hala Tripura Sundari Chedavarapu	104078.0001US3	9426

149344 7590 10/30/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER
AZPURU, CARLOS A

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
10/30/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

officeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 18100804
Applicant : Chodavarapu
Filing Date : 01/24/2023
Date Mailed : 10/30/2023

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Tim Ritter/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 18100804

IDENTIFICATION OF APPLICATION DEFICIENCIES
IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012

[X] Applicant must provide legible text for the following item(s).

- [X] Specification filed 01/24/2023, page(s) 26, 28, 34, 36-42, 44.
- [ ] Claims filed , claim(s) .
- [ ] Other: .

[ ] Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).

[ ] The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).

[ ] Applicant must provide an Abstract of the Disclosure.

[ ] The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.

[ ] Other:

The response to this notice should contain only amended papers, as the waiver of 37 CFR 1.312 is limited to corrections of documents specifically requested in the notice.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/100,804	**11/03/2023 06:22:39 PM Z ET**	**104078.0001US3**

Title of Invention

Lyophilized Compositions of Phenobarbital Sodium Salt

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9426	FILED BY	Danielle Moroz
PATENT CENTER #	63160971	FILING DATE	01/24/2023
CUSTOMER #	149344	FIRST NAMED INVENTOR	Bala Tripura Sundari Chodavarapu
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Martin Fessenmaier

Documents **TOTAL DOCUMENTS: 13**

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Notice to File Corrected Papers_2023-10-30.pdf	3	Miscellaneous Incoming Letter	104 KB
Response-02_to_Notice to File Corrected Papers of 2023-10-30.pdf	3	Miscellaneous Incoming Letter	114 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 37.pdf	1	Specification	217 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 38.pdf	1	Specification	207 KB

Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 42.pdf	1	Specification	199 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 40.pdf	1	Specification	199 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 39.pdf	1	Specification	202 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 41.pdf	1	Specification	206 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 26.pdf	1	Specification	181 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 44.pdf	1	Specification	139 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 28.pdf	1	Specification	195 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 34.pdf	1	Specification	207 KB
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 36.pdf	1	Specification	200 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

Notice to File Corrected Papers_2023-10-30.pdf	64247FFEBCFC885B770773160C81458876A7E74BFF31A384F43B09CBD70B7E08FEA59CF4315D1A49092BCB0287E8DDBA9E6BA01514C97C4854FA39CCE3711607
Response-02_to_Notice to File Corrected Papers of 2023-10-30.pdf	D00CB99FAC2307BA7CA899118B36AA830DBFFDE6CBC5C3037F01FDAAD800B576A85AB9694A959F5A628073EFAEA18A1D0A54587F04785C2090F02E202D899846
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 37.pdf	9E5D473E0D2C3BBCE9C6DC900CF2C88B462E48C6A78DD88CC297BDD64F7C575DB821888921EC60111BC047DCC8CEF57FA40A0A785BE012447988FA5E748F2123
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 38.pdf	7CF2C263477FF1CDB4E624AA98ED67379E768D2C02C2C554D8FD1699814B49D0928F44E7E34999013F3450705F4601B6C5D63A6644CEBF4B76111FF575324D28
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 42.pdf	565C2828A8D5D1033D5F95A7E5B442B812E3088D8A34BAB0B50ADDF1D11743096E049040FF5F182F1049BDB5170F6802837660A240F61631A42A2C5E6466DC3F
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 40.pdf	DE5580A4E82E7961FF62C92B37C112186E5ECDF8F6FCFC8787F59262347160399B1E9D01C17F900FEEA3C4F471A8141339BF47854A4538C25C11CBD19D76C43C
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 39.pdf	E1055EB47622EC01DA983543771CC6DE01326D659F6BAF5EDDC3A69340974D411644C9A89BFCB706DB378D4816023936FEF90D3E63EE4A35F963B29B63F7AB67
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 41.pdf	B4D11447326EF2D79A638D17A3A909231D905F6E35A3E689660C6A110F8A0D97DD121A2CB970B8080176AC9A28C48140E52569117120FCB900D1EF6600B6CC20
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 26.pdf	2F8436BEC19F0042B3CC36362B5C3AFBB3C7D55E607FD1E0B5362D1DBA56EA87E6DA72666DA2FCCDF74BA8F73251FACA6C38E7055A926269E8C800F1D0F771E2
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 44.pdf	2BD774AA1E9F516BED6BC4B501439EEB8614E2EA285CC28986C6FEA2C8BBD1D88F233173C3B7430A92A8FA810FA201612475BB28D3B30A9E16218FBF3238FCC3

Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 28.pdf	DE9D38A4B342EA779A616AA95691A92083E46FAFA2D9248E16F465DDC7EC6C29090F7622AA55D93469FFF26B3E142362DEEFEEBC4C675374F836EBEA72A1E608
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 34.pdf	624993750135731507 78CC75147DF162EC7A25E1795DDC0950C97E4567EEE202B4AD7F5EDF82664C60017357D0670B976E1D4C614CD1DFE59DF73922C441E620
Response-02_to Notice to File Corrected Papers of 2023-10-30_Page 36.pdf	44F5B698AA6EE0BF73E684C193C39264C437B1798756C5A4FA6578F01E1875A09B97246D28BF7D9F81F6CB25E490BDF0EBB7CE0AD63B2F9B37A713FC0CCD2985

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 10/30/2023
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER
AZPURU, CARLOS A

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
10/30/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

cofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04 07)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 18100804
Applicant : Chodavarapu
Filing Date : 01/24/2023
Date Mailed : 10/30/2023

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Tim Ritter/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 18100804

IDENTIFICATION OF APPLICATION DEFICIENCIES
IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012

[X] Applicant must provide legible text for the following item(s).

- [X] Specification filed 01/24/2023, page(s) 26, 28, 34, 36-42, 44.
- [ ] Claims filed , claim(s) .
- [ ] Other: .

[ ] Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).

[ ] The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).

[ ] Applicant must provide an Abstract of the Disclosure.

[ ] The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.

[ ] Other:

The response to this notice should contain only amended papers, as the waiver of 37 CFR 1.312 is limited to corrections of documents specifically requested in the notice.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl No.:	18/100,804	Examiner:	Carlos A AZPURU
First Inventor:	Bala Tripura Sundari Chodavarapu	Art Unit:	1617
Filing Date:	2023-01-24	Docket No.:	104078.0001US3
Title	Lyophilized Compositions of Phenobarbital Sodium Salt		

RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This paper responds to the Notice to File Corrected Application Papers dated 10/30/2023.

Please enter the amendments shown herein.

- Specification amendments begin on page 2.
- Remarks begin on page 3.
- 11 Replacement Pages are attached to this paper.

AMENDMENTS TO THE SPECIFICATION

Please replace pages 26, 28, 34, 36-42, and 44 with the corresponding replacement sheets 26, 28, 34, 36-42, and 44 attached to this paper.

REMARKS/ARGUMENTS

Specification Objection

The Office requested in the Notice to File Corrected Application Papers of 10/30/2023 that replacement pages 26, 28, 34, 36-42, and 44 be submitted. The Applicant herewith submits replacement sheets for pages 26, 28, 34, 36-42, and 44. No new matter has been introduced by virtue of this submission. The Applicant believes that the application is now in condition for grant.

Respectfully submitted,
Umberg Zipser LLP

Date: November 3, 2023

By: /Martin Fessenmaier Ph.D./
Martin Fessenmaier Ph.D.
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[00125] Table 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium eal. 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	**Spec.**	**Initial DOA: 06/05/20**	**Reconstituted Solution Stability after 20 hrs**	
			DOA: 06/06/2020	
			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
Note Book Reference		192065-163 to 189	192065- 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: a-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00126] Table 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031 B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)				
Test	**Specification**	**Initial**	**Reconstituted Solution Stability after 20 hrs**	
			2-8°C	**RT**
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5%	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution 1 minute after reconstitution; ND: Not Detected, NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: a-Phenylbutyrylguanidine, PEAU: Phenylethylacetylurea				

[00129] Table 10

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make: 2 mL Clear Glass Vial; Stopper: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal. API: Phenobarbital Sodium, USP Grade P			
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**	
			DOA: 03/23/2020		**DOA:05/20/2020**		**DOA: 09/04/2020**	
			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	9.6	9.6
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances 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%	0.7	0.9	1.3	1.4	1.5	1.6	2.1
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		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-Phenylbutyryliguanidine, PEAU:Phenylethylacetylurea ;								

[00130] Table 11

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**NPH1980 Fill Volume: 1.0 mL	**Date Manufactured:** 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		**Date Initiated:** 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV. **Re test Date:**		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 09/27/2019		1 Month DOA: 10/31/2019				3 Months DOA: 01/10/2020				6 Months DOA: 04/08/2020			
				RT		ACC		RT		ACC		RT		ACC	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay of Phenobarbital	90.0%-105.%	98.4	97.6	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
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%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 0.2%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031- 169 to183				192939-44 to 52				192045-46 to 85			

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

[00139] Table 17. Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

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

Ingredients	NPH1980 (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°		
	Fill Volume 1.0 mL		
	mg/mL (after reconstitution)	mg/vial	Batch Quantity (100 mL)
Phenobarbital Sodium	20	100	10.113 g
WFI/DI Water	qs	qs	Qs to 100 mL or 103.3 g

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C/60% RH (RT) & 40°C/75% RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**		**24 Months**
			DOA: 03/23/2020		**DOA: 05/20/2020**		**DOA: 09/04/2020**		**DOA: 18-MAR-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6	9.7
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2	101.2
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.9	1.3	1.4	1.5	1.6	2.1	1.8
Note Book Reference		192039-150 to 158	192085-23 to 45		192045-135 to 151		192051-84 to 122		192099-157, 159, 167, 170

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

[00145] Table 19 depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PGB, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00146] Table 19 (65 mg/vial, up to 37 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH1907	**Date Manufactured:** 02/21/2019
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C±2°C, 60% RH±5% (RT) & 40°C±2°C, 75% RH±5% (ACC)

Test	**Spec.**	**Initial DOA: 02/25/2019**	**1 Month DOA: 03/28/2019**		**3 Months DOA: 05/24/2019**		**6 Months DOA: 08/28/2019**		**15 Months DOA: 06/12/2020**	**37 Months**
			RT	ACC	RT	ACC	RT	ACC	*RT	**RT
Description	White to almost white lyophilized powder	+	+	+	+	+	+	+	+	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (65 mg/mL)	9.2-10.2	9.8	10.0	10.1	9.6	9.6	9.7	9.7	9.8	
% Assay Phenobarbital Sodium	90.0%-105.0%	99.1	98.4	99.1	98.7	97.4	100.0	99.3	96.0	
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Water Content by Karl Fischer	NMT 3.0%	0.8	1.1	1.3	1.6	1.7	1.2	2.2	2.0	
Note Book Reference		192019-41,44,45,47	192019-122, 123,126,127		192025-25,30,31,34		192031-8, 12, 14, 16, 17, 18		192051-2 to 11	

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

[00147] Table 20 depicts exemplary results for 100 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00148] Table 20 (100 mg/vial, up to 30 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**NPH1980 Fill Volume: 1.0 mL	**Date Manufactured:** 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		**Date Initiated:** 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal, Lot#NA
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 09/27/2019		1 Month DOA: 10/31/2019				3 Months DOA: 01/10/2020				6 Months DOA: 04/08/2020				30 Months DOA: 18-MAR-2022	
				RT		ACC		RT		ACC		RT		ACC		RT	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UR	T
Description	WLP	WLP	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	CCS	CCS
pH (100 mg/mL)	9.2–10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9	9.6	9.6
% Assay of Phenobarbital	90.0%–105.0%	98.4	97.6	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6	99.2	100.0
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PBG	NMT 0.2%	ND	ND	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	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 1.0%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.5	1.2	1.5	2.0	2.1	1.8
Note Book Reference		192931-91 to 103		192931 - 169 to 183				192939-44 to 52				192945-46 to 85				192899 - 127, 159, 167, 170	

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

[00149] Table 21 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00150] Table 21 (130 mg/vial, up to 37 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 130 mg/vial	**Batch#**NPH1912	**Date Manufactured:** 02/25/2019
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C±2°C, 60% RH±5% (RT) & 40°C±2°C, 75% RH±5% (ACC)

Test	**Spec.**	**Initial DOA: 02/25/2019**	**3 Month DOA: 03/28/2019**		**3 Months DOA: 05/24/2019**		**6 Months DOA: 08/28/2019**		**15 Months DOA: 06/12/2020**	**37 Months DOA: 18-MAR-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.8	10.0	9.9	9.8	9.8	9.8	9.8	10.0	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	98.3	97.1	98.3	98.3	97.9	98.8	99.4	98.3	99.2
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	0.5	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	0.5	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.6	1.3	1.2	1.1	1.3	1.9	1.4	1.4	1.5
Note Book Reference		192019-41,44,45,47	192019-122, 123,125,126		192025-25,30,31,34		192031-8,12, 14, 16, 17, 18		192051-2 to 11	192099-157, 159, 167, 170

DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution; 1 minute after reconstitution;
ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide monohydrate; PBG:6-Phenylbutyryliguanidine; PEAU:Phenylethylacetylurea

[00151] Table 22 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00152] Table 22 (130 mg/vial, up to 24 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 130 mg/vial		**Batch#**NPH2021 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial			**Date Initiated:** 02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;			
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)	

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month DOA: 03/23/2020**		**3 Months DOA: 05/20/20**		**6 Months DOA: 09/04/20**		**24 Months DOA: 18-Mar-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039- 150 to 158	192045- 27 to 45		192045- 135 to 151		192051- 84 to 122		192099-157, 159, 167, 170

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

[00153] Table 22 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00154] Table 22 (200 mg/vial, up to 22 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial	**Batch#**NPH203EA Fill Volume: 3.1 mL	**Date Manufactured:** 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated:** 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper		**Flip Off Seals:** 20mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C 60% RH (RT) & 40°C 75% RH (ACC)

Test	**Spec.**	**Initial DOA: 06/05/20**	**3 Months**		**6 Months**		**24 Months**
			DOA: 09/04/2020		**DOA: 12/11/2020**		**DOA: 11-Apr-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7	9.7	9.7	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	100.1	98.1	101.0	100.8	102.5	98.2
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.05	(BQL)
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3	1.2	1.6	1.5
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067- 78 to 88		192034- 137

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

[00155] Table 23 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%). In contrast to Table 22, this formulation was filled into the vial using a 9% saline solution. The final concentration of the saline after reconstitution in 10 mL of water for injection will be 0.9%.

[00156] Table 23 (200 mg/vial, up to 12 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial)	**Batch#**NPH2031B Fill Volume: 2.1 mL	**Date Manufactured:** 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated:** 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV:		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper		**Flip Off Seals:** 20mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C 60% RH (RT) & 40°C 75% RH (ACC)

Test	**Spec.**	**Initial DOA: 06/05/20**	**3 Months**		**6 Months**		**12 Months**
			DOA: 09/04/2020		**DOA: 12/11/2020**		**DOA: 11-Apr-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067- 78 to 88		192034- 137

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

[00157] To further investigate if the nature of the reconstitution solution would have an adverse effect on stability after reconstitution, the inventors used 65 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose to a final concentration of 1 mg/ml. In an additional set of experiments, the inventors used 130 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose or water to a final concentration of 20 mg/ml. The so reconstituted solutions were then kept under refrigeration (2-8 °C) or at standard conditions (25 °C) for the indicated times in the tables below. The levels of degradation were determined by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Once more, under all tested conditions, the stability of the so reconstituted compositions was unexpectedly high.

[00158] Table 24 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 1 mg/mL that was stored under refrigeration or at standard conditions. Under all tested conditions, 2EPMM, PBG, and PEAU remained undetectable or below

Admixture study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2020) (1 mg/mL dilution in 0.9% Saline)														
Specifications	**Tests/Time**	**Initial**	**1 hr**		**2.5 hrs**		**4 hrs**		**6 hrs**		**9 hrs**		**24 hrs**	
			2-8C	RT	**2-8C**	RT	**2-8C**	RT	**2-8C**	RT	**2-8C**	RT	**2-8C**	RT
Complies	**Description**	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	**pH (1mg/mL dilution)**	9.0	8.8	8.9	9.0	9.0	8.9	8.9	8.8	8.9	8.7	8.8	8.5	8.4
Assay 90%-105%	**Assay of Phenobarbital Sodium**	95.8	96	94.3	95.4	93.6	95.5	95.2	95.8	93.9	94.6	96.4	95.2	95.3
2EPMM NMT 0.2%	**Related Substances (%Area) 2EPMM**	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT 0.2%	**PBG**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT 0.2%	**PEAU**	BQL	ND	BQL	BQL	BQL	BQL	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	**Any unspecified degradation product @RRT 0.29**	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
	Any unspecified degradation product @RRT 0.37	0.02	0.02	0.03	0.02	0.03	0.02	0.04	0.02	0.04	0.03	0.05	0.03	0.1
NMT 1.5%	**Total degradation products**	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	0.1
Osmolality To be reported	**Osmolality (mOsmol/kg)**	288	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	286	287
CCS: Clear Colorless Solution, ND: Not Detected; BQL: Below Quantitation Limit, NP: Not performed 2EPMM: 2-ethylphenylmalonamide, monohydrate, PBG: Phenylbutyrylguanidine, PEAU Phenylethylacetylurea; BQL: Below Quantitation Limit (0.05%)														

[00162] **Table 26** depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00163] Table 26 (130 mg/vial, reconstituted to 20 mg/ml in 0.9% saline, up to 24 hrs)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

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EXAMINER	
AZPURU, CARLOS A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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PTOL-90A (Rev. 04/07)

Notice of Allowability	Application No. 18/100,804	Applicant(s) Chodavarapu, Bala Tripura Sundari	
	Examiner CARLOS A AZPURU	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the substitue spec pages filed 11/13/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-33 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

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Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

U.S. Patent and Trademark Office
PTOL-37 (Rev. 08-13)

Notice of Allowability

Part of Paper No./Mail Date 20231108

[00125] Table 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium cal. 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	**Spec.**	**Initial DOA: 06/05/20**	**Reconstituted Solution Stability after 20 hrs**	
			DOA: 06/06/2020	
			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
Note Book Reference		192085-163 to 189	192085-163-183	
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: a-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00126] Table 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031 B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)				
Test	**Specification**	**Initial**	**Reconstituted Solution Stability after 20 hrs**	
			2-8°C	**RT**
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5%	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution 1 minute after reconstitution; ND: Not Detected, NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: a-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

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11/08/2023

[00129] Table 10

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make: 2 mL Clear Glass Vial; Stopper: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal. API: Phenobarbital Sodium, USP Grade P			
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**	
			DOA: 03/23/2020		**DOA:05/20/2020**		**DOA: 09/04/2020**	
			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	9.6	9.6
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances 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%	0.7	0.9	1.3	1.4	1.5	1.6	2.1
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		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-Phenylbutyryl guanidine, PEAU:Phenylethylacetylurea ;								

[00130] Table 11

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11/08/2023

Replacement Sheet

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**NPH1980 Fill Volume: 1.0 mL	**Date Manufactured:** 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		**Date Initiated:** 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV. **Re test Date:**		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 09/27/2019		1 Month DOA: 10/31/2019				3 Months DOA: 01/10/2020				6 Months DOA: 04/08/2020			
				RT		ACC		RT		ACC		RT		ACC	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay of Phenobarbital	90.0%-105.%.	98.4	97.6	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
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%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 0.2%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031- 169 to183				192939-44 to 52				192045-46 to 85			

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

[00139] Table 17. Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

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

Ingredients	NPH1980 (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°		
	Fill Volume 1.0 mL		
	mg/mL (after reconstitution)	mg/vial	Batch Quantity (100 mL)
Phenobarbital Sodium	20	100	10.113 g
WFI/DI Water	qs	qs	Qs to 100 mL or 103.3 g

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C/60% RH (RT) & 40°C/75% RH (ACC)

Test	**Spec.**	**Initial DOA: 02/19/20**	**1 Month**		**3 Months**		**6 Months**		**24 Months**
			DOA: 03/23/2020		**DOA: 05/20/2020**		**DOA: 09/04/2020**		**DOA: 18-MAR-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6	9.7
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2	101.2
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.9	1.3	1.4	1.5	1.6	2.1	1.8
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099-157, 159, 167, 170

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

[00145] Table 19 depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PGB, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00146] Table 19 (65 mg/vial, up to 37 months)

OK TO ENTER: /C.A.A/

11/08/2023

Replacement Sheet

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH1907	**Date Manufactured:** 02/21/2019
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C±2°C, 60% RH±5% (RT) & 40°C±2°C, 75% RH±5% (ACC)

Test	**Spec.**	**Initial DOA: 02/25/2019**	**1 Month DOA: 03/28/2019**		**3 Months DOA: 05/24/2019**		**6 Months DOA: 08/28/2019**		**15 Months DOA: 06/12/2020**	**37 Months**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	***RT**	****RT**
Description	White to almost white lyophilized powder	"	"	"	"	"	"	"	"	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (65 mg/mL)	9.2-10.2	9.8	10.0	10.1	9.6	9.6	9.7	9.7	9.8	
% Assay Phenobarbital Sodium	90.0%-105.0%	99.1	98.4	99.1	98.7	97.4	100.0	99.3	96.0	
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	0.7	0.6	0.04	
Water Content by Karl Fischer	NMT 3.0%	0.8	1.1	1.3	1.6	1.7	1.2	2.2	2.0	
Note Book Reference		192019-41,44,45,47	192019-122, 123,126,127		192025-25,30,31,34		192031-8, 12, 14, 16, 17, 18		192051-2 to 11	

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

[00147] Table 20 depicts exemplary results for 100 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00148] Table 20 (100 mg/vial, up to 30 months)

OK TO ENTER: /C.A.A/

11/08/2023

Replacement Sheet

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**NPH1980 Fill Volume: 1.0 mL	**Date Manufactured:** 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		**Date Initiated:** 09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal, Lot#NA
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 09/27/2019		1 Month DOA: 10/31/2019				3 Months DOA: 01/10/2020				6 Months DOA: 04/08/2020				30 Months DOA: 18-MAR-2022	
				RT		ACC		RT		ACC		RT		ACC		RT	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UR	T
Description	WLP	WLP	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	CCS	CCS
pH (100 mg/mL)	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9	9.6	9.6
% Assay of Phenobarbital	90.0%-105.0%	98.4	97.6	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6	99.2	100.0
% Impurity 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PBG	NMT 0.2%	ND	ND	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	BQL	BQL
Any unspecified degradation product #RRT 0.37	NMT 0.2%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 1.5%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0	2.1	1.8
Note Book Reference		192031-91 to 101		192031- 165 to 183				192039-44 to 52				192035-46 to 85				192389- 127, 359, 167, 170	

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

[00149] Table 21 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00150] Table 21 (130 mg/vial, up to 37 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 130 mg/vial		**Batch#**NPH1912	**Date Manufactured:** 02/25/2019
Vial Make	2 mL Fiolax Clear Blow Back Vial			**Date Initiated:** 02/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV			
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper		**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C±2°C, 60% RH±5% (RT) & 40°C±2°C, 75% RH±5% (ACC)	

Test	**Spec.**	**Initial DOA: 02/25/2019**	**3 Month DOA: 03/28/2019**		**3 Months DOA: 05/24/2019**		**6 Months DOA: 08/28/2019**		**15 Months DOA: 06/12/2020**	**37 Months DOA: 18-MAR-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.8	10.0	9.9	9.8	9.8	9.8	9.8	10.0	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	98.3	97.1	98.3	98.3	97.9	98.8	99.4	98.3	99.2
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	0.5	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	0.5	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.6	1.3	1.2	1.1	1.3	1.9	1.4	1.4	1.5
Note Book Reference		192019-41,44,45,47	192019-122, 123,125,126		192025-25,30,31,34		192031-8,12, 14, 16, 17, 18		192051-2 to 11	192099-157, 159, 167, 170

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

[00151] Table 22 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00152] Table 22 (130 mg/vial, up to 24 months)

OK TO ENTER: /C.A.A/

11/08/2023

Replacement Sheet

Product Name	**Phenobarbital Sodium for Injection USP**, 130 mg/vial	**Batch#**NPH2021 Fill Volume: 1.05 mL	**Date Manufactured:** 01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial		**Date Initiated:** 02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV;		
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper	**Flip Off Seals:** 13mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month DOA: 03/23/2020**		**3 Months DOA: 05/20/20**		**6 Months DOA: 09/04/20**		**24 Months DOA: 18-Mar-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0%	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039- 150 to 158	192045- 27 to 45		192045- 135 to 151		192051- 84 to 122		192099-157, 159, 167, 170

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

[00153] Table 22 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00154] Table 22 (200 mg/vial, up to 22 months)

OK TO ENTER: /C.A.A/

11/08/2023

Replacement Sheet

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/vial	**Batch#**NPH2031A Fill Volume: 2.1 mL	**Date Manufactured:** 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated:** 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper	**Flip Off Seals:** 20mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	**Stability**	25°C /60% RH (RT) & 40°C /75% RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months DOA: 09/04/2020		6 Months DOA: 12/11/2020		24 Months DOA: 11-Apr-2022
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7	9.7	9.7	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	100.1	98.1	101.0	100.8	102.5	98.2
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.05	(BQL)
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3	1.2	1.6	1.5
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067- 78 to 88		192034- 137

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

[00155] Table 23 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%). In contrast to Table 22, this formulation was filled into the vial using a 9% saline solution. The final concentration of the saline after reconstitution in 10 mL of water for injection will be 0.9%.

[00156] Table 23 (200 mg/vial, up to 12 months)

Product Name	**Phenobarbital Sodium for Injection USP**, 200 mg/Vial (Phenobarbital Sodium and 9% Saline/Vial)	**Batch#**NPH2031B Fill Volume: 2.1 mL	**Date Manufactured:** 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		**Date Initiated:** 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper		**Flip Off Seals:** 20mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	**Stability**	25°C /60% RH (RT) & 40°C /75% RH (ACC)

Test	**Spec.**	**Initial DOA: 06/05/20**	**3 Months**		**6 Months**		**12 Months**
			DOA: 09/04/2020		**DOA: 12/11/2020**		**DOA: 11-Apr-2022**
			RT	**ACC**	**RT**	**ACC**	**RT**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5%	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067- 78 to 88		192034- 137

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

[00157] To further investigate if the nature of the reconstitution solution would have an adverse effect on stability after reconstitution, the inventors used 65 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose to a final concentration of 1 mg/ml. In an additional set of experiments, the inventors used 130 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose or water to a final concentration of 20 mg/ml. The so reconstituted solutions were then kept under refrigeration (2-8 °C) or at standard conditions (25 °C) for the indicated times in the tables below. The levels of degradation were determined by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Once more, under all tested conditions, the stability of the so reconstituted compositions was unexpectedly high.

[00158] Table 24 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 1 mg/mL that was stored under refrigeration or at standard conditions. Under all tested conditions, 2EPMM, PBG, and PEAU remained undetectable or below

Admixture study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2020) (1 mg/mL dilution in 0.9% Saline)														
Specifications	Tests/Time	Initial	1 hr		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs	
			2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Complies	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1mg/mL dilution)	9.0	8.8	8.9	9.0	9.0	8.9	8.9	8.8	8.9	8.7	8.8	8.5	8.4
Assay 90%-105%	Assay of Phenobarbital Sodium	95.8	96	94.3	95.4	93.6	95.5	95.2	95.8	93.9	94.6	96.4	95.2	95.3
2EPMM NMT 0.2%	Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT 0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT 0.2%	PEAU	BQL	ND	BQL	BQL	BQL	BQL	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @RRT 0.29	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
	Any unspecified degradation product @RRT 0.37	0.02	0.02	0.03	0.02	0.03	0.02	0.04	0.02	0.04	0.03	0.05	0.03	0.1
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	0.1
Osmolality To be reported	Osmolality (mOsmol/kg)	288	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	286	287
CCS: Clear Colorless Solution; ND: Not Detected; BQL: Below Quantitation Limit; NP: Not performed 2EPMM: 2-ethylphenylmalonamide, monohydrate; PBG: Phenylbutyrylguanidine; PEAU:Phenylethylacetylurea; BQL: Below Quantitation Limit (0.05%)														

[00162] **Table 26** depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00163] Table 26 (130 mg/vial, reconstituted to 20 mg/ml in 0.9% saline, up to 24 hrs)

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/100,804	**11/22/2023 04:38:25 PM Z ET**	**104078.0001US3**

Title of Invention

Lyophilized Compositions of Phenobarbital Sodium Salt

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9426	FILED BY	Danielle Moroz
PATENT CENTER #	63362703	FILING DATE	01/24/2023
CUSTOMER #	149344	FIRST NAMED INVENTOR	Bala Tripura Sundari Chodavarapu
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Martin Fessenmaier

Documents **TOTAL DOCUMENTS: 4**

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Response-03_post-allowance under Rule 312_REV001.pdf		7	-	133 KB
Response-03_post-allowance under Rule 312_REV001-A.NA.pdf	(1-1)	1	Amendment after Notice of Allowance (Rule 312)	111 KB
Response-03_post-allowance under Rule 312_REV001-CLM.pdf	(2-5)	4	Claims	95 KB
Response-03_post-allowance under Rule 312_REV001-REM.pdf	(6-7)	2	Applicant Arguments/Remarks Made in an Amendment	90 KB

Issue Fee Payment_.pdf	1	Issue Fee Payment (PTO-85B)	649 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Response-03_post-allowance under Rule 312_REV001.pdf	432955947FE40196CF138C9D9CA4D846A5E8BEC78812A9A0B1ACF099500FA9C4ED5D3B4175229F924CA0511F63C9AE7D17B4871D1458B6080873D12F60B2E4B1
Response-03_post-allowance under Rule 312_REV001-A.NA.pdf	44668D55DB8B06B6F3AD7653EE4065F5C71B61FF22D572FB2A72CFF9F76A6F508D8FE98668F5657F2AA3B20220C7A75F7ACD8DED3FCD00D3B1C32D6C9E94103B
Response-03_post-allowance under Rule 312_REV001-CLM.pdf	E7AD46685FA30D574885D0A6D54FEC0D06E60A14E7083779E93D0C399DC597FBDCA7FE529A8E8D1F5D000E237E8E24E49D5ADBC61494C0919E99BDFE1572EB0F
Response-03_post-allowance under Rule 312_REV001-REM.pdf	11872BCA7F3C2F7422A8644E702D8EEDEB290A22C4F5EE1BD63A84BACD40066C76B8EE7702799C8FC03BFD617F435C6C9EE8BB361E3BF70A118FCB5C0919B6B3
Issue Fee Payment_.pdf	20A2B2C4460559E55B07BA60F4917D819DD62E4B5286B4068657DCA01FB67B6691334105C2B9CB8BCA1A07DE9E65BC603E0A2C01BF393EC31D297F13DA9A3691

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an

international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl No.:	18/100,804	Examiner:	Carlos A AZPURU
First Inventor:	Bala Tripura Sundari Chodavarapu	Art Unit:	1617
Filing Date:	2023-01-24	Docket No.:	104078.0001US3
Title	Lyophilized Compositions of Phenobarbital Sodium Salt		

AMENDMENT UNDER 37 CFR § 1.312 ('RULE 312 AMENDMENT')

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This paper follows the Notice of Allowance dated 11/14/2023. Please enter the amendments shown herein.

- Claim amendments begin on page 2.
- Remarks begin on page 6.

AMENDMENTS TO THE CLAIMS

This listing of claims represents the current version of claims before the Office:

1-20. (canceled)

21. (previously presented) A storage stable pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized, and

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

22. (previously presented) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at 40°C for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.1% PEAU.

23. (previously presented) The pharmaceutical product of claim 21, 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.

24. (previously presented) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at 40°C for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG).

25. (previously presented) The pharmaceutical product of claim 21, wherein the composition is amorphous.

26. (previously presented) The pharmaceutical product of claim 21, wherein the composition has the property that when the composition is stored at room temperature for 24 months and then

reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains at most 0.1% phenylethylacetylurea (PEAU).

27. (previously presented) A pharmaceutical product, comprising:

a single use dose vial, and

a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial,

wherein the composition is sterile and lyophilized,

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

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

28. (previously presented) The pharmaceutical product of claim 27, 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.

29. (previously presented) The pharmaceutical product of claim 27, 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).

30. (previously presented) The pharmaceutical product of claim 27, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

31. (previously presented) The pharmaceutical product of claim 30, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).

32. (previously presented) The pharmaceutical product of claim 33, wherein the composition has the property that when the composition is stored at room temperature for 6 months and then reconstituted for injection with 10 mL of an aqueous solution to form a reconstituted composition, the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG).

33. (previously presented) The pharmaceutical product of claim 27, wherein the composition is amorphous.

34. (New) The pharmaceutical product of claim 21, 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).

35. (New) The pharmaceutical product of claim 34, wherein the composition is amorphous.

36. (New) The pharmaceutical product of claim 21, wherein the product comprises the 100 mg dose in the single use dose vial.

37. (New) The pharmaceutical product of claim 27, wherein the product comprises the 100 mg dose in the single use dose vial.

38. (New) The pharmaceutical product of claim 28, 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).

39. (New) The pharmaceutical product of claim 28, 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).

40. (New) The pharmaceutical product of claim 28, wherein the composition is amorphous.

REMARKS/ARGUMENTS

Following the Notice of Allowability dated 11/14/2023, Applicant submits an amendment under 37 CFR 1.312 to add further claims. The previously allowed claims are marked 'Previously Presented' and are not changed. The newly added claims are combinations of allowed dependent as follows, or merely narrow the independent claims as follows:

New Claim	Combination of allowed claims
34	22 + 24
35	22 + 24 + 25
36	21
37	27
38	28 + 29
39	28 + 30
40	28 + 33

Therefore, no new matter has been added and the newly added claims should be deemed allowable by virtue of their combination of prior allowed claims that further narrow the scope of the added claims. Favorable consideration is respectfully requested.

///

Request For Allowance

Claims 21-40 are pending in this application. Applicant requests allowance of all pending claims.

Respectfully submitted,
Umberg Zipser LLP

Date: November 22, 2023

By: /Martin Fessenmaier Ph.D./
Martin Fessenmaier Ph.D.
Reg. No. 46697

Umberg Zipser LLP
1920 Main Street, Suite 750
Irvine, CA 92614
Telephone (949) 679-0052
Fax (949) 679-0461

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize expendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

149346 7590 10/16/2023
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Danielle Moroz	(Typed or printed name)
/Danielle Moroz/	(Signature)
November 22, 2023	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.00001183	9426

TITLE OF INVENTION: Lyophilized Compositions of Phenobarbital Sodium Salt

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	01/16/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
AZPURU, CARLOS A	1617	424-489000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Umberg Zipser LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: NIVAGEN PHARMACEUTICALS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): SACRAMENTO, CA

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via Patent Center or EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 601823

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Martin Fessenmaier/ Date November 22, 2023

Typed or printed name Martin Fessenmaier Registration No. 46697

PTOL-85 Part B (08-18) Approved for use through 08/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/100,804	11/22/2023 04:38:25 PM Z ET	104078.0001US3

Title of Invention

Lyophilized Compositions of Phenobarbital Sodium Salt

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	9426	FILED BY	Danielle Moroz
PATENT CENTER #	63362703	AUTHORIZED BY	Martin Fessenmaier
CUSTOMER #	149344	FILING DATE	01/24/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bala Tripura Sundari Chodavarapu

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1133	E2023ALG39567472	Danielle Moroz

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
601823	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	$480.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 12/11/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
12/11/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Response to Rule 312 Communication	Application No.	Applicant(s)	
	18/100,804	Chodavarapu et al.	
	Examiner	Art Unit	AIA (FITF) Status
	CARLOS A AZPURU	1617	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 22 November 2023 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.
   f) ☐ not entered because the supplemental or corrected Application Data sheet (ADS)
      ☐ was not accompanied by a petition to accept an unintentionally delayed claim under 37 CFR 1.55 or 27 CFR 1.78;
      ☐ did not identify the information being changed in accordance with 37 CFR 1.76(c)(2);
      ☐ was not properly signed in accordance with 37 CFR 1.76(e) (or 37 CFR 1.33(b) for applications filed prior to September 16, 2012).

The added claims are in dependent form and do not add new matter or limitations not already presented in the allowed claim set.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

OK TO ENTER: /C.A.A/

11/22/2023

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl No.:	18/100,804	Examiner:	Carlos A AZPURU
First Inventor:	Bala Tripura Sundari Chodavarapu	Art Unit:	1617
Filing Date:	2023-01-24	Docket No.:	104078.0001US3
Title	Lyophilized Compositions of Phenobarbital Sodium Salt		

AMENDMENT UNDER 37 CFR § 1.312 ('RULE 312 AMENDMENT')

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This paper follows the Notice of Allowance dated 11/14/2023. Please enter the amendments shown herein.

- Claim amendments begin on page 2.
- Remarks begin on page 6.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 12/15/2023

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
12/15/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Corrected ***Notice of Allowability***	**Application No.** 18/100,804	**Applicant(s)** Chodavarapu et al.	
	Examiner CARLOS A AZPURU	**Art Unit** 1617	**AIA (FITF) Status** Yes

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address–

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the 312 Amendment filed 12/11/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-40 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/CARLOS A AZPURU/
Primary Examiner, Art Unit 1617

U.S. Patent and Trademark Office
PTOL-37 (Rev. 08-13)

Notice of Allowability

Part of Paper No./Mail Date 20231212

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/23/2024	11878076	104078.0001US3	9426

149344 7590 01/03/2024

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

IR103 (Rev. 10/09)

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Bala Tripura Sundari Chodavarapu, Davis, CA;
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APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/100,804	01/24/2023	Bala Tripura Sundari Chodavarapu	104078.0001US3	9426

149344 7590 01/23/2024

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
AZPURU, CARLOS A	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
01/23/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficeaction@appcoll.com
patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

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APPLICATION NO.	ISSUE DATE	PATENT NO.
18/100,804	23-Jan-2024	11878076

Umberg Zipser LLP
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EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/100,804

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	* 0	x =	0	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x =	0			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	664		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Derwent Innovation Patent Export, 2025-02-05 01:32:59 +0000

Search results for: PNS=(US11878076);
Collections searched: DWPI; ARIPO grant; Argentina UM; Argentina app; Armenia grant; Australia UM; Australia app; Australia grant; Austria UM; Austria app; Austria grant; Belarus UM; Belarus grant; Belgium app; Belgium grant; Brazil UM; Brazil app; Brazil grant; Bulgaria UM; Bulgaria app; Bulgaria grant; Canada app; Canada grant; China, Mainland UM; China, Mainland app; China, Mainland grant; Colombia app; Costa Rica UM; Costa Rica app; Croatia UM; Croatia app; Croatia grant; Cuba app; Cuba grant; Czech Republic UM; Czech Republic app; Czech Republic grant; Czechoslovakia grant; Denmark UM; Denmark app; Denmark grant; Estonia UM; Estonia app; Estonia grant; Eurasian (EAPO) grant; Europe (EP) app; Europe (EP) grant; Finland app; Finland grant; France app; France grant; Georgia grant; German Democratic Republic app; German Democratic Republic grant; Germany UM; Germany app; Germany grant; Greece app; Greece grant; Gulf Cooperation Council grant; Hong Kong UM; Hong Kong app; Hong Kong grant; Hungary grant; Iceland grant; India app; India grant; Indonesia UM; Indonesia app; Ireland UM; Ireland app; Ireland grant; Israel grant; Italy grant; Italy grant; Italy grant; Italy grant; Japan UM; Japan app; Japan grant; Korea UM; Korea app; Korea grant; Latvia grant; Lithuania grant; Luxembourgh app; Luxembourgh grant; Malaysia app; Malaysia grant; Mexico app; Mexico grant; Moldova UM; Moldova grant; Monaco grant; Mongolia UM; Mongolia grant; Morocco app; Morocco grant; Netherlands app; Netherlands grant; New Zealand grant; Norway app; Norway grant; OAPI grant; PCT (WO) app; Philippines UM; Philippines app; Philippines grant; Poland UM; Poland grant; Portugal UM; Portugal app; Portugal grant; Romania UM; Romania app; Romania granted; Russia UM; Russia app; Russia grant; Saudi Arabia app; Saudi Arabia grant; Serbia UM; Serbia app; Serbia grant; Singapore app; Singapore grant; Slovakia UM; Slovakia app; Slovakia grant; Slovenia UM; Slovenia grant; South Africa app; Spain UM; Spain app; Spain grant; Sweden app; Sweden grant; Switzerland app; Switzerland grant; Taiwan UM; Taiwan appl; Taiwan grant; Thailand UM; Thailand app; Thailand grant; Tunisia app; Turkey UM; Turkey app; UK app; UK grant; USSR grant; Ukraine UM; Ukraine grant; United States app; United States grant; Uruguay app; Vietnam UM; Vietnam app; Vietnam grant; Other

Table of Contents

1. US11878076B2 Lyophilized compositions of phenobarbital sodium salt

Family 1/1

1 record(s) per family

Record 1/1 US11878076B2 Lyophilized compositions of phenobarbital sodium salt

Title: Lyophilized compositions of phenobarbital sodium salt

Title - DWPI: Pharmaceutical product, comprises container enclosing single dose of lyophilized phenobarbital sodium powder; where phenobarbital sodium powder contains residual quantities of tert-butanol, isopropanol, ethanol, acetonitrile and phenobarbital sodium powder otherwise does not contain organic solvent

Priority Number: US62903511P | US17025881A | US17854914A

Priority Date: 2019-09-20 | 2020-09-18 | 2022-06-30

Application Number: US18100804A

Application Date: 2023-01-24

Publication Date: 2024-01-23

IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
A61K000919	A	A61	A61K	A61K0009	A61K000919
A61K0031515	A	A61	A61K	A61K0031	A61K0031515
A61K004702	A	A61	A61K	A61K0047	A61K004702

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
A61K0031515	A	A61	A61K	A61K0031	A61K0031515
A61K004702	A	A61	A61K	A61K0047	A61K004702
A61K000919	A	A61	A61K	A61K0009	A61K000919

Assignee/Applicant: NIVAGEN PHARMACEUTICALS INC.,Sacramento,CA,US

JP F Terms:

JP FI Codes:

Assignee - Original: NIVAGEN PHARMACEUTICALS INC.

Any CPC Table:

Type	CPC - Current - Invention	CPC - Current - Additional	Version	Office
Current Current	**A61K 9/19** A61K 31/515	-	20130101 20130101	EP; US EP; US
Current	A61K 9/0019	-	20130101	EP
Current	A61K 47/02	-	20130101	US
Original Original Original	**A61K 9/19** A61K 31/515 A61K 47/02	-	20130101 20130101 20130101	US US US

ECLA:

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.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2024-01-03	STCF	-
Description: INFORMATION ON STATUS: PATENT GRANT PATENTED CASE		
2023-12-12	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL PUBLICATIONS -- ISSUE FEE PAYMENT VERIFIED		
2023-12-05	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL PUBLICATIONS -- ISSUE FEE PAYMENT VERIFIED		
2023-12-01	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL AWAITING TC RESP, ISSUE FEE PAYMENT VERIFIED		

2023-11-24	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL PUBLICATIONS -- ISSUE FEE PAYMENT RECEIVED		
2023-11-08	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL NOTICE OF ALLOWANCE MAILED -- APPLICATION RECEIVED IN OFFICE OF PUBLICATIONS		
2023-10-12	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL NOTICE OF ALLOWANCE MAILED -- APPLICATION RECEIVED IN OFFICE OF PUBLICATIONS		
2023-09-27	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL RESPONSE TO NON-FINAL OFFICE ACTION ENTERED AND FORWARDED TO EXAMINER		
2023-06-21	STPP	-
Description: INFORMATION ON STATUS: PATENT APPLICATION AND GRANTING PROCEDURE IN GENERAL NON FINAL ACTION MAILED		
2023-02-14	FEPP	-
Description: FEE PAYMENT PROCEDURE ENTITY STATUS SET TO SMALL (ORIGINAL EVENT CODE: SMAL); ENTITY STATUS OF PATENT OWNER: SMALL ENTITY		
2023-01-24	FEPP	-
Description: FEE PAYMENT PROCEDURE ENTITY STATUS SET TO UNDISCOUNTED (ORIGINAL EVENT CODE: BIG.); ENTITY STATUS OF PATENT OWNER: SMALL ENTITY		
2023-01-24	AS	-
Description: ASSIGNMENT NIVAGEN PHARMACEUTICALS, INC., CALIFORNIA ASSIGNMENT OF ASSIGNORS INTEREST; ASSIGNORS:CHODAVARAPU, BALA TRIPURA SUNDARI; MANGALI, THIRUPATHI; SHUKLA, JAY; AND OTHERS; REEL/FRAME:062469/0169 2019-09-20		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

Litigation (US): 2024-01-23 2024 Nivagen Inc. Sun Pharma Advanced Research Company Ltd. Sun Pharmaceutical Industries Ltd. Sun Pharmaceutical Medicare Ltd. Sun Pharmaceuticals

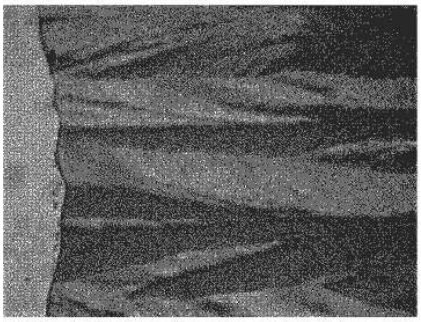
Industries Inc. Texas Eastern District Court 2:24-cv-00036

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Priority Number - DWPI: US2019903511P | US202025881A | US2022854914A | US2023100804A
Priority Date - DWPI: 2019-09-20 | 2020-09-18 | 2022-06-30 | 2023-01-24
Assignee - Current US: NIVAGEN PHARMACEUTICALS INC.

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Lyophilized Compositions of Phenobarbital Sodium Salt

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
11878076	18100804	01/24/2023	01/23/2024

Payment Window Status

WINDOW	STATUS	FEES
3.5 Year	Not Open	Not Due

No maintenance fees are due at this time. 3.5 year window opens on 01/23/2027.

Window	First Day to Pay	Surcharge Starts	Last Day to Pay	Status	Fees
3.5 Year	01/23/2027	07/24/2027	01/24/2028	Not Open	Not Due
7.5 Year	01/23/2031	07/24/2031	01/23/2032	Not Open	Not Due
11.5 Year	01/23/2035	07/24/2035	01/23/2036	Not Open	Not Due

Patent Holder Information

Customer # 149344

Entity Status SMALL

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UNITED STATES