

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SUN PHARMACEUTICALS INDUSTRIES INC.,

Petitioner

v.

NIVAGEN PHARMACEUTICALS, INC.,

Patent Owner

IPR2025-00893

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

**DECLARATION OF ALEXANDER M. KLIBANOV, Ph.D., IN SUPPORT
OF PATENT OWNER'S PRELIMINARY RESPONSE**

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I, Alexander M. Klibanov, declare as follows:

I. INTRODUCTION

1. I have been retained by Patent Owner Nivagen Pharmaceuticals, Inc. (“Nivagen” or “Patent Owner”) as an expert in the above-captioned U.S. Patent and Trademark Office (“PTO”) proceeding to provide opinions on certain technical issues relating to the validity of the claims of U.S. Patent No. 11,878,076 B2 (“the ’076 patent”) raised by the Petitioner Sun Pharmaceuticals Industries, Inc. (“Sun Pharma” or “Petitioner”).

2. I have been asked by Nivagen’s counsel (“counsel”) to consider and give my opinion on how a person of ordinary skill in the art at the time of the ’076 patent’s invention (“POSA”) would understand the patent itself, its file history (including Ex. 1003, provisional U.S. patent application No. 62/903,522; Ex. 1004, U.S. patent application No. 17/025,881 (“the ’881 App.”); and Ex. 1002, U.S. patent application No. 18/100,804 (“the ’804 App.”)), the references Sun Pharma relies upon for its Petition, and other materials relied upon by Sun Pharma. I have also been asked by counsel to respond to certain arguments in Sun Pharma’s Petition and to Dr. Raj Suryanarayanan’s opinions provided in his Declaration (Ex. 1015) in support of Sun Pharma’s Petition. In conducting my analysis herein, I have reviewed the documents cited throughout this Declaration.

3. In particular, I have been asked to evaluate whether the prior art references Petitioner submitted, singly or in combination, disclosed to or taught a POSA the subject matter claimed in the '076 patent. In my opinion, they did *not*.

4. I have previously submitted a declaration in a patent litigation between the same two parties in the U.S. District Court for the Eastern District of Texas, Case Number 24-00036, which litigation I understand from counsel is ongoing, to provide my opinions on the construction of the claim term “composition” in the '076 patent. My claim construction declaration from that litigation was filed with Patent Owner’s Brief in Support of Request for Discretionary Denial (Paper 7) as Ex. 2016.

5. I am being compensated at my standard consulting rate for the time spent on this matter. My compensation does not depend on the opinions rendered or the outcome of this or any other proceeding, including the Federal District Court litigation mentioned above.

II. QUALIFICATIONS

6. I am currently a Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology (“M.I.T.”), where I taught and conducted research for over 40 years. From 2014 to 2019 (and also from 2007 to 2012), I held the Novartis Endowed Chair Professorship at M.I.T. From 2012 to 2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in

Chemistry. Prior to that, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, I was an Assistant Professor, then an Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

7. I obtained my M.S. in Chemistry from Moscow University in Russia in 1971 and Ph.D. in Chemical Enzymology (a branch of Medicinal Chemistry) from the same university in 1974. Thereafter, I was a Research Chemist at Moscow University's Department of Chemistry for three years. From 1977 to 1979, following my immigration to the United States, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

8. Over the last 55 years as a practicing chemist, I have extensively researched, published, and lectured in many areas of chemistry, including formulation and medicinal chemistry.

9. During my 40 years as a M.I.T. professor, I taught numerous undergraduate and graduate courses in various areas of chemistry, including general, organic, physical, and biological chemistry.

10. I have earned numerous prestigious professional awards and honors. For example, I was elected to the U.S. National Academy of Sciences (considered

among the highest honors that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer). I am also a Founding Fellow of the American Institute for Medical and Biological Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society (the largest professional society in the world), as well as the International Enzyme Engineering Prize.

11. I currently serve on the Editorial or Advisory Boards of over a dozen scientific publications, including "Open Access Academic Books in Chemistry," "Applied Biochemistry and Biotechnology," "Nanocarriers," "Biotechnology and Bioengineering," "Journal of Biological Chemistry and Molecular Pharmacology," "Recent Patents in Biotechnology," "Archives of Medical Biotechnology," "Current Pharmaceutical Biotechnology," "Open Journal of Pharmacology," and "International Journal of Drug Design, Delivery, and Safety."

12. I have published over 315 scientific papers in various areas of chemistry, and I am also a named inventor of 32 issued United States patents and of a number of pending ones. Many of those publications and patents have dealt with preparation, formulation, stability, stabilization, and evaluation of biologically

active compounds, such as active pharmaceutical ingredients. I also have given over 370 invited lectures, including many distinguished named lectureships, at scientific conferences, universities, and corporations all over the world. According to a recent Stanford University-led study, the overall impact of my published work places me in the top 0.01% of all scientists in the world.

13. In addition to my research and teaching activities at M.I.T., I have consulted widely for pharmaceutical companies. Of particular relevance to the present patent litigation is my broad practical experience with both solid and liquid pharmaceutical formulations, injectable therapeutic drugs, lyophilization (also called freeze-drying), and stability (including analysis of impurities) and characterization of drug substances and products.

14. I also have founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies and of many others.

15. As of September 20, 2019 (the priority date of the '076 patent; *see* Ex. 1001 at field (60) on the cover page of the patent), I at least met (and indeed exceeded) the background and qualifications requirements for a POSA with respect to the '076 patent, as outlined below.

16. My *Curriculum vitae*, filed with Patent Owner's Preliminary Response and this Declaration as Ex. 2030 summarizes my education and

academic experience. Among other things, it lists all my professional publications and patents.

III. THE FIELD OF ART AND THE QUALIFICATIONS OF A POSA

17. I have been advised by counsel that there are multiple factors relevant to determining the level of ordinary skill in the pertinent art, including the educational level of active workers in the field at the time of the invention, the sophistication of the technology, the type of problems encountered in the art, and the prior-art solutions to those problems.

18. The field that pertains to the '076 patent “relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity.” (Ex. 1001, '076 patent, at 1:17-19.) This field involves pharmaceutical formulation technology and practice, pharmaceutical stability and impurities levels, and pharmaceutical product development and manufacture.

19. I understand from counsel that Petitioner raised an issue concerning the priority date of the '076 patent and, in particular, whether the priority date for at least some of the patent claims is in 2019 or 2022. However, I do not believe that the definition of a POSA in the field would differ between 2019 and 2022; hence this dispute does not affect my opinions expressed in this Declaration.

20. In my opinion, a POSA at the time of the claimed invention would have had a Ph.D. degree in chemistry, biochemistry, or pharmaceuticals, and at least

2 years of experience (or less education but more years of experience, i.e., an M.S. with at least 3-5 years of experience, or a B.S. with a minimum of 6 years of experience) with pharmaceutical drug product formulation, analysis, development, optimization, and manufacture, including experience with processes and techniques for minimizing impurities in, and improving the stability of, pharmaceutical drug products during their manufacture and storage.

21. A POSA in particular would have experience with designing and/or manufacturing lyophilized pharmaceutical compositions.

22. Petitioner relies on the Declaration of Dr. Suryanarayanan with respect to its definition of a POSA. (Ex. 1015 at ¶ 17.) I disagree with some aspects of Dr. Suryanarayanan's POSA definition, including that a POSA would have the ability "to consult with ... experts" (as opposed to only with ordinarily skilled artisans) and to the extent that any documents to be relied upon by a POSA are not necessarily limited to publicly available ones. However, my opinions on the disclosures of the '076 patent, its prosecution history, and the prior art references Petitioner brought will not change whether Dr. Suryanarayanan's or my definition is adopted by the Patent Trial and Appeal Board ("PTAB").

IV. CLAIM CONSTRUCTION

25. As noted above, I was involved in the claim construction process in the Texas Federal District Court '076 patent litigation between Nivagen and Sun Pharma (collectively, “the parties”). In that case, the parties ultimately disagreed on the construction of just one claim term of the '076 patent, which is “composition.” The parties took the following positions with respect to this claim term:

<u>Claim Term</u>	<u>The Parties' Positions</u>
“composition” (all claims)	<u>Nivagen</u> : plain and ordinary meaning <u>Sun Pharma</u> : plain and ordinary meaning (no dispute on that meaning), but disclaiming “formulations that contain organic solvents or preservatives”

26. Sun Pharma had also argued that several claim terms of the '076 patent were “indefinite.” (Ex. 2003 (Sun Pharma’s Amended Invalidity Contentions served in the Texas Federal District Court litigation), at 324-27.) However, by the time I submitted my expert declaration for the claim construction

process in the litigation, (Ex. 2016,) I understand from counsel that Sun Pharma was no longer making those “indefiniteness” assertions.

27. In the IPR Petition, Sun Pharma took the following position: “Petitioner does not believe any claim terms [of the ’076 patent] require specific construction for the purpose of deciding the Grounds 1-3 challenges set forth in this Petition.” (Petition at 13.) Dr. Suryanarayanan also stated in his Declaration that “the claim elements [of the ’076 patent] include straightforward language and are readily understandable according to their ordinary and customary meaning—without the need to inject specialized definitions or substitute terminology.” (Ex. 1015 at ¶ 87.)

28. Therefore, unless the Federal District Court construed the claim term “composition” differently and the PTAB would adopt the Court’s claim construction, I believe that everyone in this IPR proceeding agrees that, in the context of the ’076 patent claims, the claim term “composition” has a plain and ordinary meaning, without any additional disclaimer aiming to narrow that meaning (as, for example, attempted by Sun Pharma; *see* ¶ 21 above). I also agree with Dr. Suryanarayanan that the other claim terms in the ’076 patent have their “ordinary and customary meaning[s]” that “are readily understandable” to a POSA.

29. I opined during the Texas Federal District Court litigation that the plain and ordinary meaning of the claim term “composition” is “a mixture of

pharmaceutical ingredients that is suitable for pharmaceutical purposes.” (Ex. 2016, at ¶ 21.) Furthermore, as expressly taught in all of the ’076 patent claims, the claim term “composition” is a “lyophilized” (and hence necessarily solid) mixture, which a POSA would understand to contain residual **bound** solvents, such as water or organic solvents previously present in the aqueous “bulk solution;” such residual solvents can also originate from the active pharmaceutical ingredient (“API”) and/or the excipients in the lyophilized composition. (*Id.* at ¶¶ 22-23.)

30. The lyophilization process involves freezing the bulk solution and then drying it under vacuum to cause sublimation and to leave behind a so-called solid “cake” that is structurally distinctive and contains a detectable bound solvent content (i.e., water or an organic solvent), which can originate from an intended excipient (solvent, whether water or organic) added to make the bulk solution, or from any residual bound water or organic solvent carried over from one or more solid components that were dissolved in the bulk solution but then re-appeared in a solid state in the lyophilized composition, or from both.

31. Those are still my opinions on the meaning of the claim term “composition” in the ’076 patent, and I incorporate by reference my aforementioned claim construction declaration, including my opinions and all supporting information discussed therein.

V. ADDRESSING GROUND 1 (PIF/PARKER/WEST-WARD COMBINATION)

A. THE PIF, PARKER, AND WEST-WARD REFERENCES FAIL TO DISCLOSE ALL CLAIM ELEMENTS IN THE '076 PATENT

32. Ground 1 of Sun's IPR Petition is based on a combination of PIF (Ex. 1009), Parker (Ex. 1012), and West-Ward (Ex. 1013). (Petition at 4-5.)

33. **PIF (Ex. 1009)** is a "pharmaceutical interview form" for a product called "Nobelbar." (Petition at 13.) PIF appears to be from July 2010. (PIF at cover page, at bottom.) According to Petitioner, "PIF teaches a lyophilized drug containing 274 mg of phenobarbital sodium (or 250 mg as phenobarbital) per vial for intravenous injection." (Paper 1, Petition at 13-14.)

34. Petitioner, relying on Dr. Suryanarayanan's opinion, then stated that "PIF teaches a lyophilized injection [*sic*] composed of phenobarbital sodium only, without additives." (*Id.* at 14, citing Ex. 1015 (Dr. Suryanarayanan's Declaration) at ¶ 97.) I do not quite agree with this statement regarding the composition of Nobelbar. Having reviewed the PIF reference (Ex. 1009, the English translation from the Japanese original), I do not believe that a POSA would reasonably conclude from this reference that the Nobelbar product was necessarily "composed of phenobarbital sodium only." Petitioner links the "no additive" to "phenobarbital sodium only," but I see disclosures in the PIF reference indicating that "no additive" does not necessarily mean "API only."

35. For example, on page 4 of PIF, section IV-5, the reference discloses that the drug was tested for “related substances, moisture, loss on drying, endotoxin, ... foreign insoluble matter, insoluble particulates” The testing results were not disclosed, however, except for the general comment that “[o]ther than moisture content, there was *no change* in any of the test item under any of the storage conditions” (emphasis added). In my opinion, a POSA would not conclude from these statements that the Nobelbar product was necessarily “composed of phenobarbital sodium only,” as Petitioner and Dr. Suryanarayanan did. For example, just because “there was no change” in “related substances” does not necessarily mean that no such substances were present to begin with. In other words, it cannot be excluded that the composition also contained “related substances,” “moisture” (water content), or potentially other bound solvents (undefined) measured by “loss on drying” (residual solvents in the lyophilized composition that could originate from the bulk solution or the API itself).

36. Furthermore, the fact that “moisture” and “loss on drying” are two separate items Nobel Pharma tested would suggest to a POSA that bound solvents other than water (i.e., one or more organic solvents) could have been present in the lyophilized composition. Such an organic solvent could have been used in the bulk solution in addition to water and, if so, it is unclear what the PIF authors

meant by “does not contain any additives” (PIF at 1, I-2 (4)) or “additive not including.” (*id.* at 4, IV-2 (2)).

37. The PIF lyophilized product was packaged in “[c]olorless glass, [with] butyl rubber stopper.” (*Id.* at 9, section IV-14.) PIF expressly disclosed that increased moisture of the lyophilized product was detected during storage stability testing, but that the increased moisture content “was thought to originate from the rubber stopper of the vial”—without any experimental data to prove this hypothesis. (*Id.* at 4, section IV-5.) Even if true, however, a POSA would understand that if water could leak from the rubber stopper, then other materials (e.g., lubricants) potentially can, too; but that possibility was neither mentioned nor controlled by Nobel Pharma.

38. Even if the Nobelbar product was made with water and the API as the only intended ingredients of the bulk solution, and no leachables were introduced during lyophilization, a POSA still would not conclude that the lyophilized product was necessarily “composed of phenobarbital sodium only.” PIF disclosed testing for “related substances,” both in the storage stability testing context mentioned above and after dissolving the lyophilized product in water. When dissolved in water, “at the start,” there was already 0.09% of “related substances” that were actually tested for (*id.* at 5, section IV-6), which is not an insignificant amount considering, for example, that many of the ’076 patent claims require a level of “no

more than 0.05%” for a single degradation impurity. The “0.09%” initial declared (and thus the minimum for this sample) impurity level appears to be the only quantitative data in PIF that might be able to indicate what the purity level of the lyophilized product actually was. Assuming that the dissolution and the testing reflected in section IV-6 (*id.* at 5) were done quickly, which should have been the case, the lyophilized Nobelbar composition contained significant amounts of substances other than just phenobarbital sodium. A POSA would recognize that the “0.09%” number in PIF is the minimal amount for all impurities in the samples tested and not necessarily the total amount of all impurities therein because the HPLC testing done by Nobel Pharma may not have been designed for, or have reflected, the level of all impurities in Nobelbar.

39. In general, a POSA would not find PIF to be particularly informative on the impurity profile of the Nobelbar product described therein. Because there are no protocols in the document for the testing of “related substances” in sections IV-5 or IV-6, a POSA would be unable to tell what substances were detected or quantified in any of the testing PIF describes. There must have been some work done by Nobel Pharma to determine how to detect “related substances;” indeed, PIF does disclose some “adulterants that may be contaminants.” (*Id.* at 9, section IV-9.) These are “[a]nalogous substances that may be introduced as contaminants in the manufacturing process of the bulk drug,” which could be part of the “related

substances” Nobel Pharma tested for and reported in sections IV-5 and IV-6, but a POSA reading PIF could not know for sure.

40. The three manufacturing-process-related “analogous substances” shown in PIF at 9, section IV-9, are 5-methyl-5-phenyl-barbitaric acid, 2-phenylbutyrylurea, and 2-phenylbutyric acid. Of the three, 2-phenylbutyrylurea (also called phenylethylacetylurea) is the same compound known as “PEAU” in the ’076 patent, but the other two are *not* the specific degradation impurities recited in the ’076 patent claims, which are 2EPMM (2-ethyl-2-phenylmalonamide) and PBG (alpha-phenylbutyrylguanidine). There is no indication in PIF that either 2EPMM or PBG was even tested for, let alone what their levels were. If these two degradants were not accounted for during the storage stability testing disclosed in PIF, then their levels were simply unknown; hence whether the levels would increase during the testing, let alone by how much, would also be unknown.

41. Although the PEAU degradant could have been tested for by Nobel Pharma, there is no specific evidence in PIF that it was. There is also no indication in PIF that the testing results or conclusions would be representative of the commercial Nobelbar product sold. In particular, nothing in PIF indicates to a POSA that the product samples tested were indeed pulled from commercial batches, how many samples were tested, and/or what was done to ensure that the

results were representative. It is also noteworthy that there is no experimental-error range attached to any of the numbers in the results tables in section IV-6.

42. A POSA would find the “no change” conclusion in IV-5 of PIF to be less than definitive because there is no disclosure of what criteria Nobel Pharma used to come to that conclusion. It is possible, for example, that “no change” just meant “did not cross a threshold” for each of the parameter tested—and that threshold could be rather high. Water-facilitated degradation was acknowledged as a major concern for phenobarbital products. (*See id.* at 3 (the phenobarbital sodium API “gradually decomposes when left in moist air”); *see also* my discussion below regarding the disclosures of the Parker reference.) Therefore, it is concerning to see PIF reporting on page 4 that for the same study (1) “there was no change in any of the test items under any of the storage conditions” and (2) “[m]oisture content tended to increase compared to the start of the study.” No matter where the moisture came from, once the lyophilized composition was exposed to it, a POSA would necessarily expect some hydrolysis or other water-related degradation of the phenobarbital sodium API to occur. Over prolonged time periods, and some of the samples were reportedly tested over **36 months**, it is indeed hard to believe that the results actually showed “no change” in “related substances,” unless only a few related substances were tested for and they did not arise from water-facilitated degradation. (*Id.* at 4.)

43. If the “no change” conclusion just meant “did not cross a threshold,” there was no information provided in PIF on what that threshold was and what chemical compounds were subject to it. Nor is there any indication that Nobel Pharma had ever set a threshold for any “related substance[.]” or an analogous substance for its commercial phenobarbital sodium product. The Nobelbar product was approved in Japan in 2008 (*id.* at 35), but apparently it was never approved or sold in the United States. Nobelbar expressly was a response to a long-term need for the lack of intravenous phenobarbital products in Japan. (*Id.* at 1.) Petitioner and Dr. Suryanarayanan did not comment on what the drug approval criteria were in Japan under these circumstances. Likewise, PIF’s disclosure that the product had a 3-year “use-by date” (*id.* at 35, section X-1) does not tell a POSA how stable it was, either in general or specifically in terms of the levels of the degradants PEAU, 2EPMM, or PBG upon storage conditions that are claimed in the ’076 patent.

44. Some of the dependent claims of the ’076 patent recite that “the composition [of phenobarbital sodium] is amorphous.” There is no disclosure, however, that the phenobarbital sodium composition in Nobelbar is amorphous to any degree. The only disclosure in PIF regarding the dosage form’s physical appearance states “[w]hite mass or powder, lyophilized injection.” (*Id.* at 4, section IV-1.) While PIF does say “[w]hite crystals or crystalline powder,

odorless, bitter taste” in section III-2 on page 3, that section is actually a subpart of the “III. Active Ingredients” section. Therefore, a POSA would understand that the “white crystals or crystalline powder” description refers to the phenobarbital sodium API that was used to make the Nobelbar drug through a lyophilization process, i.e., a starting material (a drug substance) and not the lyophilized drug product itself.

45. **Parker (Ex. 1012)** is U.S. Patent Application Publication No. 2017/0143719, published on May 25, 2017. Parker appears to claim priority to Provisional Application No. 62/258,000, filed on November 20, 2015 (Ex. 1012 at [0001]). My analysis of Parker is the same whether Parker was deemed available to a POSA in 2015 or 2017.

46. Parker teaches alcohol- and preservative-containing liquid solution formulations of phenobarbital sodium, which are obviously ***not*** lyophilized compositions or products. (*Id.* at [0002].) Parker discloses that “[a] number of phenobarbital injection USP products are currently available on the US and international markets for various treatments, including as a medication for partial and generalized tonic-clonic seizures as well as for treatment of neonatal seizures.” (*Id.* at [0003].) As Parker was filed and published several years ***after*** the PIF reference was published, the “phenobarbital injection USP products” should include Nobelbar.

47. Parker then states that the problem its inventors sought to solve was “to minimize or preferably eliminate any [degradation] impurities in commercial phenobarbital sodium injection formulations,” and further, that “[t]he solution to the problem then easily becomes removal of water from the formulation.” (*Id.* at [0004]-[0005].) Note that the “removal of water” clause here unequivocally refers to minimizing water content in a *liquid solution* formulation, *not* to a lyophilization process. (*Id.*)

48. Parker then discloses that the storage-related degradants PEAU and 2-phenylbutyric acid (PBA, which is also disclosed in PIF as a manufacturing-process-related “analogous substance[.]”) are “typical impurities for phenobarbital solutions that include water as part of the solvent system.” (*Id.* at [0006].) A POSA reading this disclosure thus would understand that minimizing the water content in a liquid solution formulation is a way to reduce “typical [degradation] impurities” in such aqueous liquid formulations, including PEAU and PBA.

49. After specifically naming the degradants PEAU and PBA, Parker states that “[c]urrently, the limits for such impurities in commercially marketed pharmaceutical products are up to 10% of PEAU and up to 1.0% of PBA.” (*Id.* at [0006].) These percentages pertain to the contents of the impurities after 2 years of storage at room temperature. (*Id.*) Although this sentence and the % numbers address liquid solution phenobarbital products, they clearly reflect the rather lax

standards for the purity of phenobarbital commercial products in general at the time.

50. Parker mentions that “[o]ther possible degradation products of phenobarbital sodium can result from other conditions, such as reactions with base, oxidation or subjecting the compound to heat.” (*Id.* at [0007].) Parker’s Table 1 following this paragraph shows a number of “degradation products of phenobarbital sodium” and how they can be generated. In particular, 2EPMM is shown to be a result of a reaction with a base, upon oxidation, or upon heating, while PBG is shown to form upon a reaction with a base or oxidation.

51. Of these different degradation mechanisms, Parker addresses only hydrolysis and discusses prior art’s “solvent mixtures” containing reduced water contents as informative. (*Id.* at [0008]-[0015].) In particular, Parker discloses PCT publication WO 2006/125774 dealing with a formulation of the drug topiramate “that has a low water content to prevent hydrolysis of the active and to extend the storage life of the formulation.” (*Id.* at [0012].) Parker concludes its Background section discussion by noting that “the inclusion of significant amounts of water in a phenobarbital sodium formulations [*sic*] is not desirable as it will likely result in the formation of undesirable amounts of impurities. ... The present invention now addresses the need for stable, essentially impurity-free formulations.” (*Id.* at [0016].)

52. A POSA would understand that Parker was disclosing a solution to the problem of phenobarbital sodium degradation specifically by *hydrolysis*. There is no disclosure in Parker of any attempt to solve any problems of oxidation, reactions with a base, or exposure to heat. In fact, Parker describes “the present invention” as “advantageously” having a pH of between 9 and 12, which is a strongly basic pH range. (*Id.* at [0017].)

53. Furthermore, after Parker defines the term “stable” as used therein to cover “the same or less total impurities when exposed to a wider range of system parameters, i.e., oxygen head space, pH, and temperature”, it continues with “[i]n particular, the stable formulations of the present invention have been found to exhibit 1% of less, preferably 0.8% or less of hydrolysis impurities.” (*Id.* at [0029].) Notably, only the degradants PEAU and PBA are described in Parker as examples of hydrolysis impurities, and not 2EPMM or PBG focused on in the ’076 patent claims. (*See id.* at [0030], *see also id.* at [0006]-[0007].) The enhanced stability of the Parker invention was demonstrated by “a substantial reduction of PEAU and PBA impurities.” (*Id.* at [0035] (“no more than 0.8% of PEAU impurity after two years storage at room temperature” and no “detectable amount of PBA after the same period”).)

54. Parker explained how its invention worked: “This reduction in water content leads to the prevention or significant reduction of impurities as the amount

of water is insufficient to cause any significant hydrolysis of the phenobarbital ring.” (*Id.* at [0036].)

55. Parker claims a phenobarbital sodium solution for injection comprising, among other things, “propylene glycol in an amount of between 620 and 830 mg/mL.” (*Id.* at 7, claim 1.) The resultant claimed “solution contains no more than 0.8% of phenyl ethyl acetyl urea (PEAU) impurity after two years storage at room temperature.” (*Id.*)

56. **West-Ward (Ex. 1013)** appears to be the contents of a web page that was “updated 08/11.” (Ex. 1013 at 1/11.) West-Ward refers to “Phenobarbital Sodium Injection, USP,” which “is a sterile solution for intramuscular or slow intravenous administration as a long-acting barbiturate. Each mL contains phenobarbital sodium either 65 mg or 130 mg, alcohol 0.1 mL, propylene glycol 0.678 mL and benzyl alcohol 0.015 mL in Water for Injection; hydrochloric acid added, if needed, for pH adjustment. The pH range is 9.2-10.2.” (*Id.* at 1/11, 10/11 (formulation information).)

57. West-Ward’s liquid solution formulation with a large amount of propylene glycol (which is similar in this respect to the formulation disclosed in Parker) was not designed, and might be unsuitable, for a lyophilization process. Instead, it was meant to be stored as a liquid solution and administered to patients without a reconstitution step.

58. There is no disclosure on how stable the West-Ward phenobarbital sodium liquid product was or what impurity profile it had either in general or specifically regarding the degradants PEAU, 2EPMM, and PBG upon storage.

59. In my opinion, Petitioner and Dr. Suryanarayanan are both mistaken in their assertions that PIF, Parker, and West-Ward, combined, disclose all of the elements of the '076 patent claims. Following the list of limitations in the Petition, starting on page 19, I discuss below what is missing from all three references that Sun Pharma relies on for Ground 1 of its Petition. I start with **claim 1** of the '076 patent:

Element of Claim 1	Is it in PIF?	Is it in Parker?	Is it in West-Ward?
[1pre] A storage stable pharmaceutical product, comprising:	No. There is no disclosure of the impurity profile after storage or even of the assay % of the API. Moisture content was found to rise upon storage, which should lead to hydrolysis.	No. The PEAU threshold after storage is set at 0.8%, which is much higher (i.e., corresponding to far lower drug stability) than in the '076 patent claimed product. The 2EPMM or PBG	No. A similar formulation (i.e., a liquid solution) to Parker. No disclosure of product's storage stability or its impurity profile.

		levels are not even addressed.	
[1a] a single use dose vial	No disclosure of “a single use.”	No disclosure of “a single use.”	No disclosure of “a single use.”
[1b] a composition comprising a 65 mg dose, a 100 mg dose, a 130 mg dose, or a 200 mg dose of phenobarbital sodium, in the single use dose vial	No. The dose of phenobarbital sodium is 274 mg. No disclosure that the vial is a single use dose vial.	No disclosure of “a single use dose vial.”	No disclosure of “a single use dose vial.”
[1c] wherein the composition is sterile and lyophilized, and	Yes.	No. This is a liquid solution product not designed for lyophilization.	No. This is a liquid solution product not designed for lyophilization.
[1d] wherein the	No. The product contained	No. No assay % of phenobarbital	No. No assay % of phenobarbital

composition comprises no less than 98% phenobarbital sodium.	significant amount of “related substances.” No assay % of phenobarbital sodium is disclosed.	sodium is disclosed.	sodium is disclosed.
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60. **Claims 2, 3, 4, and 6** of the '076 patent each directly depends from claim 1 and adds a “PEAU impurity amount upon storage” claim element.

Additional Elements in Claims 2, 3, 4, and 6, respectively	Is it in PIF?	Is it in Parker?	Is it in West-Ward?
[2a] wherein the composition has the property that when the composition is stored at 40° C. for 6 month 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	No. No disclosure of storage stability in terms of the amount of PEAU after storage.	No. No “reconstitution” for a liquid solution product. Furthermore, the “stability” described has the threshold of “no more than 0.8%” PEAU	No, for the same reasons as Parker. In fact, since it is prior art to Parker, the PEAU level in West-
[3a] wherein the composition has			

the property that when the composition is stored at room temperature for 6 month 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		after storage, i.e., many times higher than the $\leq 0.1\%$ or $\leq 0.05\%$ levels recited in these claims.	Ward should be higher than the " $\leq 0.8\%$ " level after storage disclosed in Parker.
[4a] wherein the composition has the property that when the composition is stored at 40° C. for 6 month 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			
[6a] wherein the composition has the property that when the composition is stored at room temperature for 24 month 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			
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61. **Claim 5** of the '076 patent also directly depends from claim 1, with the added claim element “wherein the composition is amorphous.” PIF does not disclose or suggests that the lyophilized product is amorphous. Parker and West-Ward both disclose a liquid product, which cannot possibly be “amorphous,” which is a concept used to describe a solid material.

62. **Claim 6** of the '076 patent was addressed above.

63. **Claim 7** of the '076 patent is independent and recites “[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).”

64. Claim 7 is similar to claim 3 of the '076 patent, except that the PEAU content limit after 6 months of storage at room temperature is set at “no more than 0.1%” in claim 7, as opposed to “no more than 0.05%” in claim 3. Similar to the analysis for claims 1 and 3 above, none of PIF, Parker, or West-Ward discloses the elements of “a single use dose vial,” the specific claimed amounts of phenobarbital sodium, “no less than 98% phenobarbital sodium,” or the “0.1% PEAU” impurity limit after storage and reconstitution.

65. **Claim 8** of the '076 patent directly depends from claim 7, but lowers the PEAU upper limit after 6 months of storage at room temperature to 0.05%. This additional element in claim 8 was not disclosed by PIF, Parker, or West-Ward. Parker discloses that the PEAU level in the “stable” liquid formulation is no more than 0.8% after 24 months at room temperature, which would correspond to no more than at least 0.2% after 6 months at room temperature.

66. **Claim 9** of the '076 patent also directly depends from claim 7, with the added element that, after 6 months of storage at room temperature and subsequent reconstitution, “the reconstituted composition contains no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM).” PIF does not disclose 2EPMM, let alone any amount thereof, in its reconstituted lyophilized composition. PIF disclosed “0.09%” of unspecified “related substances” when its lyophilized composition was dissolved in water. (PIF at 5.) Parker, on the other

hand, did disclose 2EPMM as a degradation product of phenobarbital that can be formed through a reaction with a base, upon oxidation, or as a result of heating, but failed to disclose 2EPMM as a hydrolysis degradation product like PEAU or PBA. (Parker at [0006]-[0007], [0030].) Parker's teaching is to reduce water content in a liquid formulation by replacing it with an organic co-solvent in order to minimize the hydrolysis of phenobarbital that generates PEAU or PBA. But there is no teaching or suggestion in Parker on how to prevent or even reduce the formation of 2EPMM to any level. West-Ward contains no disclosure of 2EPMM.

67. **Claim 10** of the '076 patent also directly depends from claim 7, with the added element that, after 6 months of storage at room temperature and subsequent reconstitution, "the reconstituted composition contains no more than 0.05% of alpha-phenylbutyrylguanidine (PBG)." PIF does not disclose either PBG or any amounts of PBG in a reconstituted lyophilized composition. PIF does disclose "0.09%" of unspecified "related substances" when the lyophilized composition was dissolved in water. (PIF at 5.) Parker, on the other hand, does disclose PBG as a degradation product of phenobarbital that can be formed through a reaction with a base or upon oxidation, but does not disclose PBG as a hydrolysis degradation product like PEAU or PBA. (Parker at [0006]-[0007], [0030].) Parker's teaching is to reduce water content in a liquid formulation by replacing it with an organic co-solvent in order to minimize the hydrolysis of phenobarbital

that generates PEAU or PBA. There is no teaching or suggestion in Parker on how to prevent or reduce the formation of PBG to any level. West-Ward contains no disclosure of PBG.

68. **Claim 11** of the '076 patent directly depends from claim 10 and adds an element that the 2PEMM level after 6 months of storage at room temperature and subsequent reconstitution is “no more than 0.05% of 2EPMM.” The analysis presented above regarding claims 9 and 10 applies to claim 11.

69. **Claim 12** of the '076 patent directly depends from claim 7, with the added element that “the composition is amorphous.” None of PIF, Parker, or West-Ward discloses an amorphous composition.

70. **Claim 13** of the '076 patent directly depends from claim 12 and adds an element that, after 6 months of storage at room temperature and subsequent reconstitution, “the reconstituted composition contains no more than 0.05% of ... PBG.” As stated above regarding claim 9, this PBG level upon storage is not disclosed anywhere in PIF, Parker, or West-Ward. Parker notes that PBG is a degradation product of phenobarbital, but not formed through hydrolysis. Therefore, the reduction of water content as a “solution” to the phenobarbital hydrolysis problem does not involve reducing or even monitoring the level of PBG upon storage.

71. **Claim 14** of the '076 patent directly depends from claim 1, with the added element that the composition after storage at 6 months at room temperature and subsequent reconstitution contains no more than 0.05% of any of PEAU, 2EPMM, or PBG. Petitioner made a vague argument on page 34 of the Petition regarding this “storage stability as shown by low PEAU, 2EPMM, PBG levels i.e. not more than 0.05% for each” additional element in claim 14. I address this argument below.

72. Regarding the degradant PEAU level after storage, PIF, Parker, and West-Ward are either silent on it or set the PEAU level many times higher than the 0.05% (or 0.1%, for that matter) threshold after storage recited in the '076 patent claims. PIF did not disclose what the PEAU level is in the lyophilized composition. PIF’s categorical statement that “related substances” level did “no[t] change” after storage (for up to 36 months) is not specific to PEAU and especially not credible if the “related substances” that were tested included PEAU. (PIF at 4.) This is because the moisture content in the lyophilized composition disclosed in PIF admittedly increased upon storage, and PEAU is a product of phenobarbital’s hydrolysis. (*Id.*) As stated above, the “no change” language in section IV-5 of PIF could refer to a certain threshold that was not exceeded. It could be akin to the term “satisfactory,” but the criteria used to say so are undefined in PIF.

73. Furthermore, when the Nobelbar product was dissolved in water, 0.09% of “related substances” were detected in the phenobarbital sodium solution “[a]t the start,” and that level more than doubled to 0.19% after 6 hours at room temperature and then more than doubled again to 0.49% after 24 hours under the same conditions. (*Id.* at 5.) A POSA cannot tell what “related substances” were tested for, but this rapid rise in an aqueous solution indicates that the “related substances” here included hydrolysis degradation products, such as compounds like PEAU. The available data in PIF, therefore, suggest that the PEAU level was potentially as high as 0.09% “[a]t the start,” i.e., immediately upon reconstitution from the lyophilized composition, and would further increase rapidly upon exposure to water. The PIF data certainly do *not* suggest to a POSA that, after a storage for 6 months or longer, the PEAU level in Nobelbar, tested upon reconstitution similar to what was done to generate the data in PIF (page 5, section IV-6) would stay at “no more than 0.05%” or even at $\leq 0.1\%$.

74. PIF suggested that a component of the Nobelbar product, “the rubber stopper of the vial”, may be a source of the leaked moisture for the lyophilized phenobarbital sodium powder in the vial. (*Id.* at 4.) If so, hydrolysis of the API will necessarily occur upon storage despite dry nitrogen in the headspace. Its extent, however, is unknown because PIF reported that “there was no change in any of the test items under any of the storage conditions”—a conclusion that, in my

opinion, would be hardly credible to a POSA at least with respect to phenobarbital sodium's hydrolysis products like PEAU.

75. Furthermore, a POSA would have no reason to set the PEAU level at “no more than 0.1%”, let alone at $\leq 0.05\%$, because Parker's “stable” liquid formulation allows as much as 0.8% of PEAU after 24 months of room-temperature storage. (Parker at [0017].) There is no teaching in Parker that a level that is just a small fraction of the “0.8%” allowed level would be desirable or even attainable. Indeed, Parker discloses that the prior art products contained up to **10%** of PEAU; therefore, even the “0.8%” PEAU level was deemed very advantageous in comparison. (*Id.* at [0006].) There is no teaching in Parker (or in West-Ward, which is a similar liquid product) on how to reduce PEAU levels to “no more than 0.1%” or $\leq 0.05\%$ after 6 months of storage at room temperature (let alone after a longer duration or at a higher temperature). Nor does Parker suggest to a POSA that it would be actually possible.

76. The lack of any prior art disclosure, or a suggestion, regarding 2EPMM and PBG levels after storage is even more acute compared to the PEAU situation. Among PIF, Parker, and West-Ward, Parker is the only reference that even mentions 2EPMM or PBG, but its disclosure is that those two degradants can be formed by reacting phenobarbital with a base, or upon its oxidation, or, for 2EPMM, by exposing to heat. (Ex. 1012 at [0007].) There is no disclosure on

how to minimize the formation of these two degradation impurities upon storage of any phenobarbital sodium formulation or to what level. The entire Parker reference focused on reducing hydrolytic degradation of the API in a liquid formation by replacing with an organic co-solvent, which does not even concern 2EPMM or PBG according to the disclosures in Parker.

77. None of PIF, Parker, or West-Ward suggests a level of “no more than 0.05%” (or $\leq 0.1\%$) after storage for either 2EPMM or PBG. And none of these three references suggests that such a level of 2EPMM or PBG would be even attainable in a phenobarbital sodium composition.

78. **Claim 15** of the '076 patent directly depends from claim 14, with an added element, “wherein the composition is amorphous.” As discussed above, none of the PIF, Parker, and West-Ward references discloses a composition that is amorphous or even ever uses this term.

79. **Claim 16** of the '076 patent directly depends from claim 1, with the added element that “wherein the product comprises the 100 mg dose in the single use dose vial.” None of PIF, Parker, or West-Ward discloses the specific amount of API in a single use dose vial.

80. **Claim 17** of the '076 patent directly depends from claim 7, with the added “100 mg dose in the single use vial” claim element. Again, none of PIF, Parker, or West-Ward discloses this claim element.

81. **Claim 18** of the '076 patent directly depends from claim 8, with an added element that, after storage for 6 months at room temperature and subsequent reconstitution, the 2EPMM level is “no more than 0.05%”. For the reasons stated above regarding claims 8, 9, and 14, the 2EPMM level after storage was never disclosed, or even suggested, by PIF, Parker, or West-Ward.

82. **Claim 19** of the '076 patent also directly depends from claim 8, with an added element that, after storage for 6 months at room temperature and subsequent reconstitution, the PBG level is “no more than 0.05%”. For the reasons stated above regarding claims 8, 10, and 14, the PBG level after storage was never disclosed, or even suggested, by PIF, Parker, or West-Ward.

83. **Claim 20** of the '076 patent also directly depends from claim 8, with an added element that “the composition is amorphous.” As discussed above, this claim element is not disclosed by PIF, Parker, or West-Ward, none of which even uses this term.

84. To summarize, the following elements (which is the vast majority of them) from the claims of the '076 patent are *missing* from all of the disclosures in PIF, Parker, and West-Ward. (In fact, the only claim elements that are *not* missing are “sterile” and “lyophilized” (only in PIF).)

- “A storage stable pharmaceutical product” meeting the criteria on the PEAU, 2EPMM, and/or PBG degradation impurity levels;

- High purity in terms of API's assay percentage ($\geq 98\%$ of the intended amount of phenobarbital sodium in the product or composition);
- Each of the degradant thresholds after long-term storage: $\leq 0.1\%$ PEAU (or $\leq 0.05\%$), $\leq 0.05\%$ PBG, and/or $\leq 0.05\%$ 2EPMM;
- “The composition is amorphous”;
- Specific doses of phenobarbital sodium (65 mg, 100 mg, 130 mg, or 200 mg) in “a single use dose vial.”

B. THERE IS NO MOTIVATION TO MODIFY OR COMBINE PIF, PARKER, AND WEST-WARD TO ARRIVE AT THE INVENTION CLAIMED BY THE '076 PATENT

85. In my opinion, there would be no motivation for a POSA to modify the prior art disclosures or combine the teachings of the PIF, Parker, and/or West-Ward references. And even if a POSA were to somehow do so, there would be no teaching on how to arrive at “[a] storage stable pharmaceutical product” that is lyophilized and contains both a high purity phenobarbital sodium API (at least a 98% assay percentage) and very low levels of specific degradation impurities after prolonged storage at room or higher (such as 40° C) temperatures.

86. PIF, for example, discloses a lyophilized preparation of phenobarbital sodium that “[a]t the start” contains 0.09% of (undisclosed) “related substances” when dissolved in water. (PIF at 5.) PIF also suggests to a POSA that such a level of “related substances” was good enough. The Nobelbar product was said to be

“stable” and could be used for up to three years when “[s]tore[d] at room temperature.” (*Id.* at 35.)

87. In fact, PIF does not suggest any careful control of impurities. It does not disclose any PEAU levels upon any length of storage. The cryptic statement of “no change” for certain unspecified “related substances” is hardly credible to a POSA, especially when it is also acknowledged that the moisture content of the lyophilized phenobarbital sodium formulation did increase over time. PIF did not even mention the degradation impurities 2EPMM or PBG. It also did not disclose their presence or levels upon any storage conditions or why these two impurities (specified in the ’076 patent claims) should be focused on and/or controlled. Nor did PIF disclose how a POSA could prevent, or at least minimize, degradation pathways that generate these two impurities. And, in contrast to the ’076 patent claims, PIF certainly did not disclose that the levels of PEAU, 2EPMM, and PBG even after a multi-month storage at 40° C could be reduced to as low as “no more than 0.05%”.

88. Nobelbar has been approved in Japan since 2008. The PIF reference itself appears to be from 2011. Yet, in 2015 or 2017, i.e., several years later, the Parker inventors still did *not* turn to PIF or Nobelbar in a quest to solve the stated problem of hydrolysis-related degradation impurities (such as PEAU and PBA) in phenobarbital sodium products. In particular, Parker (or West-Ward) did not even

try to make highly pure, low-degradant, *lyophilized* phenobarbital sodium. Therefore, the actual, real-life events before the 2019 invention claimed in the '076 patent, which a POSA would have been aware of, refute Petitioner's speculation that "a POSA in 2019 would have known and naturally combined PIF, Parker, and West-Ward to make a shelf-stable, highly-pure, sterile, lyophilized, amorphous phenobarbital sodium composition having minimal impurities, including PEAU, 2EPMM, and PBG" (Petition at 16.)

89. In fact, Parker claims to have solved the problem of phenobarbital stability (in terms of hydrolytic degradation) in prior liquid-solution commercial products available by 2015. West-Ward, which discloses a commercial product available at least in 2011, appears to have a similar liquid-solution formulation to Parker and adds nothing of substance to the Parker disclosures. With respect to a few years passed between Parker and the '076 patent invention, Petitioner points to no reference that would teach modifying the Parker liquid-solution formulation into a lyophilized product. In fact, that would not even be possible because Parker (like West-Ward) requires a predominant amount of co-solvent excipients to reduce the water content in a liquid formulation and the resultant formulation is not designed, and may be even unsuitable, for any lyophilization process.

90. Furthermore, Parker boasted that the invention claimed therein reduced the "up to 10% PEAU" degradant contents upon storage in prior products

to “no more than 0.8%.” Parker expressly deemed this reduction a success and called the resulting product “stable” with no suggestion to reduce this level still further, let alone that a much lower level of $\leq 0.1\%$ or even $\leq 0.05\%$ of PEAU after a long-term storage would even be attainable.

91. Therefore, Parker (and West-Ward, which is similar) contains three levels of *teaching away* from the '076 patent invention. One, Parker points to an improved liquid formulation as the solution to the storage instability problem (and specifically with regard to the degradant PEAU) in prior phenobarbital products. Parker thus teaches a POSA away from making a storage-stable lyophilized phenobarbital sodium composition.

92. Two, Parker expressly deems formulations containing even 0.8% of PEAU after 2 years of storage at room temperature to be “stable”. With that level (which in hindsight was very high compared to what the inventors of the '076 patent achieved) reached, there is nothing in Parker (or in West-Ward, or in any other prior art I am aware of) to motivate a POSA to get far lower still (e.g., to $\leq 0.1\%$ or even $\leq 0.05\%$) PEAU degradant levels after storage at 40° C for 6 months (e.g., claim 2 of the '076 patent) or after 2 years at room temperature (e.g., claim 6 of the '076 patent). And I see nothing in PIF to suggest to a POSA that such a low level of PEAU would even be attainable.

93. Three, although Parker disclosed the degradants 2EPMM and PBG, they were stated to be generated by a reaction with a base, or upon oxidation, or by heating, but not specifically by hydrolysis. The only hydrolytic degradants Parker was concerned with were PEAU and PBA, with the latter impurity is not even claimed in the '076 patent.

94. To summarize, Parker teaches a markedly different direction for tackling the storage instability problem for phenobarbital sodium products compared to the '076 patent. If anything, a POSA following Parker's teachings would try to modify the Parker *liquid* formulation to achieve better storage stability. However, even if a POSA were to make a stable *lyophilized* composition, (s)he would have no reason to reduce the PEAU level to $\leq 0.1\%$ or even to $\leq 0.05\%$ after a long-term storage and would not know whether such a drastically lower degradation impurity levels after a long-term storage would be possible because: (1) PIF disclosed 0.09% as the initial level of "related substances" in a lyophilized product, and (2) Parker expressly calls a phenobarbital formulation "stable and essentially impurity-free" even if it contains as much as 0.8% of PEAU after a 2-year storage at room temperature. A POSA following Parker would also be led away from addressing the levels of the 2EPMM and PBG degradation impurities in a phenobarbital sodium composition because, while

disclosing them, Parker did nothing to minimize them (to any level), nor suggested that it would be advantageous to do so.

95. A POSA reviewing a combination of PIF, Parker, and West-Ward, therefore, would understand that: (1) there had been a recognized product storage instability problem in all phenobarbital sodium products before the publication of Parker in 2017, which would include at least the West-Ward product, and probably Nobelbar (because the latter has to be a part of the “a number of phenobarbital injection USP products ... currently available on the US *and international markets*” (Parker at [0003], emphasis added), including those “used to control status epilepticus” disclosed in Nobelbar; (2) the previous problem of storage instability of phenobarbital sodium compositions had been solved by Parker; (3) the solution for that problem involved a liquid formulation containing large amounts of co-solvent excipients and was unrelated to, and drastically distinct from, any lyophilized composition; and (4) the storage “stability” contemplated by Parker in 2017 (and in the field of art in general at the time) permitted a much higher level of the PEAU degradant than those claimed in the '076 patent and included no requirement for the low levels of 2EPMM and PBG after any long-term storage.

96. To summarize, PIF, Parker, and/or West-Ward lack disclosures of most of the '076 patent claim elements. The Petitioner's asserted combination of the prior art references fails to provide a motivation for a POSA to arrive at the

storage-stable, lyophilized composition of phenobarbital sodium with very low specific degradation impurity levels disclosed and claimed in the '076 patent.

C. PETITIONER'S REFERENCES PROVIDE A POSA WITH NO REASONABLE EXPECTATION OF SUCCESS

97. The PIF/Parker/West-Ward combination proposed by Sun Pharma fails to convey to a POSA a reasonable expectation of success any more than any of these three prior art references individually (which none of them does in my opinion).

98. As discussed above, Parker never even came close to contemplating the very low levels of degradants formed after a long-term storage claimed in the '076 patent. Furthermore, Parker taught that there were multiple degradation pathways generating 2EPMM and PBG upon storage but did not address how to prevent, or even reduce, most of those degradation mechanisms.

99. The West-Ward reference does not deal with any either qualitative or quantitative aspects of phenobarbital sodium degradation upon long-term storage, thereby providing a POSA with no help or encouragement in achieving stringent specific stability characteristics claimed in the '076 patent (such as “no more than 0.05%” of PEAU, 2EPMM, or PBG after a 6-month storage at room temperature or even at the elevated temperature of 40° C). Nor would a POSA have a reason to expect that West-Ward's liquid phenobarbital sodium product or the liquid solution formulation described in Parker could be lyophilized.

100. With respect to the PIF reference, as discussed above, not even qualitative, much less quantitative, breakdown of its “related substances” into specific phenobarbital sodium degradants, let alone PEAU, 2EPMM, or PBG in particular, is disclosed therein.

101. Thus, PIF could not possibly make a POSA hopeful in a quest to achieve onerous and specific stability characteristics claimed in the ’076 patent (exemplified in the preceding paragraph), especially given that the lyophilized Nobelbar product already contained 0.09% of the unspecified but tested-for “related substances” to begin with, i.e., prior to any storage.

102. Moreover, PIF expressly acknowledged that (1) the “[m]oisture content tended to increase” upon storage of the lyophilized Nobelbar product even under dry nitrogen in the vial’s headspace (PIF at 4), and (2) the phenobarbital sodium API is “[h]ygroscopic and gradually decomposes when left in moist air” (*id.* at 3). These facts would hardly contribute to POSA’s expectations of success in achieving a highly storage-stable lyophilized phenobarbital sodium product claimed in the ’076 patent.

**VI. ADDRESSING PETITIONER’S GROUNDS 2 AND 3
(ANTICIPATION AND OBVIOUSNESS BASED ON THE ’608
PUBLICATION)**

**A. THE ’608 PUBLICATION SUPPORTS THE CLAIMS OF THE
’076 PATENT UNDER THEIR ORDINARY AND CUSTOMARY
MEANINGS**

103. I have been asked by counsel to address the disclosures in U.S. Patent Application Publication No. US 2021/0085608 A1 (the “’608 Publication,” which is Ex. 1005). According to the Petition, the ’608 Publication is the published version of an “original application” that is the grandparent of the ’076 patent. (Petition at 2-3.) That grandparent application filed in 2020 (which is Ex. 1004) is in term based on a provisional patent application filed in 2019, which is Ex. 1003. As mentioned above in ¶ 2, I have reviewed both Ex. 1003 and Ex. 1004 in addition to Ex. 1005. Therefore, my analysis of the disclosures in the ’608 Publication would be the same if I had cited to substantively identical portions of Ex. 1004 instead.

104. Specifically, I was asked, and ultimately answered in the affirmative, whether the disclosures in the ’608 Publication provide a POSA with adequate written description for the claims of the ’076 patent.

105. I understand that Petitioner made two main arguments on why the ’608 Publication ostensibly did not support the “full scope” of the ’076 patent claims. (Petition at 42-49.) First, because “the original applications lack written

description for compositions containing an organic solvent.” (*Id.* at 42.) Second, because “the original applications lack written description for compositions having crystalline phenobarbital sodium.” (*Id.* at 44.) Petitioner cited Dr. Suryanarayanan’s Declaration for support, in particular Ex. 1015 at ¶¶ 204-209 (for the “organic solvent” argument) and *id.* at ¶¶ 210-216 (for the “crystalline” argument).

106. My analysis started with a review of the actual claim language of the ’076 patent, before comparing it with the disclosures in the ’608 Publication and addressing Petitioner’s invalidity allegations. None of the ’076 patent claims address any presence or absence of “organic solvents.” Instead, the claims recite “[a] pharmaceutical product comprising ... a composition comprising ... phenobarbital sodium” with further limitations on the API assay % ($\geq 98\%$) and certain degradation impurity levels after specified long-term storage. (*See* Ex. 1001 at claims 7-13 and 17-20, which I recited and analyzed above in Part V.A.) Claim 1 of the ’076 patent and the claims dependent from it (i.e., claims 2-6 and 14-16) also require the “pharmaceutical product” to be “storage stable.” (*Id.*) As discussed above, the storage stability in the ’076 patent is greatly improved upon the prior art, ultimately reaching below the recited stringent degradation impurities thresholds after exposure to specified long-term storage conditions. Thus in that

regard the “storage stable” limitation recited in claim 1 and its dependent claims is similar to the degradation impurities levels recited in claims 7-13 and 17-20.

107. Petitioner “agrees to apply the broader plain and ordinary meaning in this proceeding” for what the claim language of the ’076 patent means. (Petition at 13, fn. 2.) Dr. Suryanarayanan also stated that he applied the “ordinary and customary meaning” to the claim language. (Ex. 1015 at ¶ 87.) I agree with him that a POSA reading the ’076 patent claims would understand their meaning to be “ordinary and customary.”

108. Therefore, it should be straightforward for a POSA to make a comparison of the actual ’076 patent claim language with the ’608 Publication and consequently to assess the written support for the ’076 patent claims in the ’608 Publication. It is my opinion that a POSA would recognize disclosures of “[a] pharmaceutical product” (which is “storage stable”) with the recited phenobarbital sodium API assay %, as well as the PEAU, PBG, and 2EPMM degradation impurity levels after long-term storage, throughout the ’608 Publication. Neither Petitioner nor Dr. Suryanarayanan appears to be disputing this point, i.e., that the ’608 Publication discloses “[a] pharmaceutical product” that is “storage stable” and displays the recited $\geq 98\%$ phenobarbital sodium level and the very low degradation impurity levels after specified long-term storage.

109. Instead, both Petitioner and Dr. Suryanarayanan commented on the “full scope” of the ’076 patent claims and argued that the ’608 Publication must disclose “compositions containing an organic solvent” and “crystalline phenobarbital sodium” in order to provide written support for those claims of the ’076 patent that are *silent* to these requirements. (*See, e.g.*, Petition at 42-49; Ex. 1015 at ¶¶ 204, 210.) I disagree for the reasons explained below.

110. I understand from counsel that Patent Owner will address in its Preliminary Response whether this “full scope” argument is legally correct. I have been asked to address, *assuming* that this “full scope”-based analysis is legally relevant, whether the ’608 Publication provides to a POSA adequate written support for claim terms “compositions containing an organic solvent” and “crystalline phenobarbital sodium.” After reviewing the ’608 Publication, my answer to this inquiry is “yes” on both elements, as detailed below.

B. THE ’608 PUBLICATION PROVIDES WRITTEN DESCRIPTION FOR COMPOSITIONS CONTAINING AN ORGANIC SOLVENT

111. First, the ’608 Publication provides general disclosures of compositions that can contain an organic solvent. The “Field of the Invention” disclosed in the ’608 Publication (Ex. 1005 at [0002]), for example, is “compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water.” No distinction is drawn in that “Field of the Invention” paragraph on whether or not

the “lyophilized Phenobarbital Sodium” contains a residual bound organic solvent. A POSA reading this paragraph would, therefore, see no reason why the lyophilized “compositions” cannot contain such a residual organic solvent.

112. The “Summary” section of the ’608 Publication begins with: “Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium composition.” (*Id.* at [0010].) Again, there is no restriction as to whether the composition can contain an organic solvent, and thus a POSA would understand this statement to be inclusive.

113. In addition, the “Summary” section of the ’608 Publication discloses “[m]ethods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition,” which “result in a lyophilized powder” with certain levels of the degradation impurity PEAU after a specified long-term storage. (*Id.* at [0013].)

114. The “Summary” section of the ’608 Publication then describes various “embodiments” and “aspects” of the invention in paragraphs [0014] through [0026]. These disclosures end in an apparent concluding paragraph, which states, “[t]herefore, the inventors also contemplate lyophilized Phenobarbital Sodium.” (Ex. 1005 at [0027].) Again, this is an inclusive statement containing no restriction on whether the lyophilized Phenobarbital Sodium can contain any residual bound organic solvent.

115. Beginning in paragraph [0029] up until the claims on page 18, the '608 Publication discloses “[v]arious objects, features, aspects, and advantages” and “detailed description of *preferred embodiments*, along with the accompanying drawings.” (*Id.* at [0028], emphasis added.) As discussed below, a POSA would understand that these disclosures also do not limit whether the lyophilized phenobarbital sodium composition of the invention can contain any residual bound organic solvent at least because they expressly concern only preferred (as opposed to all possible) embodiments of the '608 Publication.

116. I have been informed by counsel that, legally, the claims in an “original application” are considered disclosures which can provide to a POSA written description support for the patent claims issued from a later, related application. Claim 1 in the '608 Publication recites “[a] pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium.” (Ex. 1005 at 18.) A POSA reading this claim would understand that, once again, the “composition” may or may not contain a residual bound organic solvent. It provides written support for similarly drafted claims (which are all silent on an “organic solvent” clause) in the '076 patent claims.

117. Dr. Suryanarayanan repeatedly cited and emphasized one sentence from the '608 Publication in his Declaration. (Ex. 1015 at ¶¶ 204-205.) It should be stressed that the sentence in question (underlined by me below) appears in the

middle of the following long paragraph in the '608 Publication, which in turn resides in the "Detailed Description" section of the '608 Publication. (Ex. 1005 at [0101].)

[0101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in FIG. 5D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% PEAU, and no detectable amount of 2EPMM or PGB 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.

118. In my opinion, Dr. Suryanarayanan’s Declaration fails to properly address the presence of residual bound organic solvents in lyophilized compositions. (Ex. 1015 at ¶¶ 202-209.) He discussed organic solvents that were intentionally added as “co-solvents” to a bulk solution for the subsequent lyophilization process, such as “isopropanol, tert-butanol, ethanol, and acetonitrile.” (*Id.* at ¶ 203.) He also pointed to the exclusion of organic solvents in “the presently disclosed formulation” (which, in fact, would be understood by a POSA to be a reference to a bulk solution rather than a lyophilized composition) from a single specific embodiment described in paragraph [0101] of the ’608 Publication. (*Id.* at ¶ 204 (Dr. Suryanarayanan citing to “Ex-1003 [the ’511 Provisional Application] at 19 (¶[0078]); Ex-1004 [the ’881 Application which later published as the ’608 Publication] at 210 (¶[00101])” (which is the same as Ex. 1005 at [0101])).)

119. Dr. Suryanarayanan also addressed organic solvents in either a bulk solution or a liquid solution formulation. (Ex. 1015 at ¶¶ 205, 207.) Finally, he opined that “[a] lyophilized phenobarbital sodium composition containing organic solvents was disclosed *for the first time* in the ’914 CIP application, filed on June 30, 2022.” (*Id.* at ¶ 208 (emphasis added).) Yet, the ostensible “first time

disclosure” he pointed to is discussing organic solvents used as co-solvents in a **bulk solution**, and **not** as residual bound organic solvents in a lyophilized solid composition. (*Id.*)

120. The lack of any discussion of residual organic solvents in a lyophilized solid composition, as opposed to in a bulk solution, makes Dr. Suryanarayanan’s opinions regarding how a POSA would under the disclosures of the ’608 Publication misleading. In fact, the ’608 Publication discloses that the invented “composition” is a “lyophilized” (and hence necessarily solid) mixture, which a POSA would generally understand to contain residual **bound** solvents, such as water or organic solvents previously present in the aqueous “bulk solution.” As explained above, the lyophilization process involves freezing the bulk solution and then drying it under vacuum to cause solvent sublimation, resulting in a so-called solid “cake.” The “cake” that results from a lyophilization process typically contains a detectable content of residual bound solvents (i.e., water or an organic solvent previously present in the bulk aqueous solution).

121. An important point Dr. Suryanarayanan appears to miss is that the residual bound solvent in the lyophilized cake can be directly from the solvent previously added to the bulk solution **or can come from individual intended ingredients**, such as the API and/or excipients (i.e., therapeutically inactive ingredients). If an ingredient (whether the API or excipients) were made with an

organic solvent in the manufacturing process, then some of the solvent may be carried over and remain (albeit to a minimal, but still detectable, degree) in the lyophilized cake being bound to it. Dr. Suryanarayanan seems to disregard that, whether or not an organic solvent is added as an intentional co-solvent to a bulk solution, the resulting lyophilized cake can nevertheless contain some organic solvent in a bound state because the API or another excipient can bring in an organic solvent used in the prior manufacturing process, for example, by forming a complex with it or as a solvate.

122. Therefore, a POSA reading the '608 Publication would understand that the “lyophilized phenobarbital sodium” disclosed therein can contain a residual bound organic solvent, and this is true even when some embodiments in the Publication disclose excluding an organic solvent as an intentionally added co-solvent in the bulk solution formulation.

123. To reiterate, paragraph [0028] of the '608 Publication expressly states that “[v]arious objects, features, aspects, and advantages [of the invention] will become more apparent from the *following detailed description of preferred embodiments*, along with the accompanying drawings [i.e., figures].” (Ex. 1005 at [0028] (emphasis and underlining added).) Therefore, a POSA would necessarily recognize the contents of the “Detailed Description” section of the '608

Publication, including paragraph [0101] and the underlined sentence therein, to be describing *preferred* (as opposed to *all possible*) embodiments of the invention.

124. In paragraph [0101] of the '608 Publication quoted above, the first sentence describes 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 [i.e., room temperature].” (Emphasis added.) The paragraph then describes certain properties of this particular *preferred embodiment*, which is “a lyophilized Phenobarbital Sodium.” Notably, a POSA would recognize that in these sentences of paragraph [0101], the word “formulation” was *not* used to describe a lyophilized solid cake but rather to describe its predecessor bulk solution.

125. Paragraph [0101] also describes the amorphous property of “a storage-stable lyophilized Phenobarbital Sodium” by referring to Figures 5 of the '608 Publication. A POSA would understand the description of “a storage-stable lyophilized Phenobarbital Sodium” and its amorphous properties in this paragraph to be specific to the embodiment that corresponds to the data shown in Figures 5: “[w]ith reference to FIGS. 5B-5C, the lyophilized Phenobarbital Sodium is amorphous.”

126. The underlined sentence above, repeatedly quoted and emphasized by Dr. Suryanarayanan in ¶¶ 204-205 of his Declaration, as well as also focused on at

page 43 of the Petition, describes “the presently disclosed *formulation*” (emphasis added) as “not contain[ing] any organic solvents or preservatives,” without referring to a “lyophilized” phenobarbital sodium *composition*, in contrast to every single one of the preceding sentences in the same paragraph [0101].

127. Immediately after this underlined sentence, paragraph [0101] continues on to state that “the *resulting lyophilized* Phenobarbital Sodium forms below the quantitation limit [of certain degradation impurities] when reconstituted in water after storage of the lyophilized Phenobarbital Sodium [under certain storage conditions]” (emphasis added).

128. A POSA reading this language in paragraph [0101], with the opening sentence of the paragraph stating that the method produces “a storage-stable lyophilized Phenobarbital Sodium,” the reference to Figures 5, and then the phrase “the resulting lyophilized Phenobarbital Sodium” that immediately follows the underlined sentence, would understand that the term “formulation” discussed here refers to the bulk solution subsequently used for the lyophilization process, and *not* to the lyophilized composition that results from the process; therefore, the underlined sentence does *not* concern the presence of residual bound organic solvents in the lyophilized cake.

129. A bulk solution “formulation” undergoes the lyophilization process and results in a lyophilized composition. A POSA would recognize that paragraph

[0101] of the '608 Publication disclosed a *preferred embodiment* with a lyophilization method that does not involve a bulk solution with intentionally added organic co-solvents.

130. The underlined sentence in paragraph [0101] discusses a “formulation,” which generally could mean either a “liquid formulation” or a “lyophilized formulation” in the '608 Publication (*see, e.g.*, Ex. 1005 at [0103], title of Table 3). However, a POSA reading the entire disclosure of the '608 Publication would understand that when the inventors wanted to refer to a *lyophilized composition*, they said so unambiguously, e.g., “the presently disclosed 65 mg [of] *lyophilized* Phenobarbital Sodium *composition*.” (*Id.* at [0103] (emphasis added).)

131. A POSA reading the '608 Publication thus would have no reason to understand the “[t]he presently disclosed formulation” underlined sentence in paragraph [0101] referring to a *preferred embodiment* (or in any other part of the '608 Publication for that matter) as *limiting*, rather than merely *adding details* to, the entire disclosure of the Publication.

132. Finally, several additional express statements in the '608 Publication's specification provide further support to my conclusions made above concerning the proper, non-limiting role of the underlined sentence in paragraph [0101]. Both Dr. Suryanarayanan and Petitioner appear to turn a blind eye to all these statements.

133. For example, paragraph [0127] of the '608 Publication teaches that “[t]he use of any and all examples ... 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.” The same paragraph also cautions a POSA that “[n]o language in the specification should be construed as indicating any non-claimed element essential to the practice of the claimed invention.” And, to reiterate, none of the claims of the '608 Publication (or of the '076 patent) even mentions any organic solvents (or preservatives), much less requires the absence of “any organic solvents or preservatives.”

134. Likewise, paragraph [0128] of the '608 Publication asserts that “[t]he 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 items should be interpreted in the broadest possible manner consistent with the context.” These disclosures further confirm that Petitioner’s and Dr. Suryanarayanan’s assessments of the role of the underlined sentence in paragraph [0101] of the '608 Publication is incorrect. In my opinion, Petitioner and Dr. Suryanarayanan fail to read that sentence in the context of the '608 Publication as a whole and myopically cherry pick that document instead.

135. Dr. Suryanarayanan also went outside the '608 Publication and discussed statements made during the prosecution of the '881 Application (which published as the '608 Publication), which he attributed to the Patent Owner. (Ex. 1015 at ¶ 207.) However, the Patent Owner's statement discussed by Dr. Suryanarayanan was referring to claims from a different patent (i.e., not from the '076 patent) which recite a method of lyophilization that does not use organic solvent as an intended co-solvent *in the bulk solution*. (*Id.*) The statement compares the "instantly claimed method" to the disclosure in Parker, which, as discussed above, is a liquid solution formulation. (*Id.*) In other words, this is a liquid-to-liquid comparison. It has no bearing on the meaning and scope of the disclosures in the '608 Publication with respect to the *lyophilized composition*.

136. In conclusion, because the '608 Publication clearly discloses a lyophilized phenobarbital sodium composition (and includes a claim for it) without restriction as to the presence or absence of any residual bound organic solvent (which is the only kind of an organic solvent that can exist in a properly made, stable, lyophilized cake), a POSA reading the '608 Publication will find adequate written description support for all claims of the '076 patent. Nothing in the '608 Publication or any other material Petitioner and Dr. Suryanarayanan asserted would change this understanding, as discussed above.

C. THE '608 PUBLICATION PROVIDES WRITTEN DESCRIPTION FOR COMPOSITIONS CONTAINING CRYSTALLINE PHENOBARBITAL SODIUM

137. Dr. Suryanarayanan points to disclosures of “amorphous” lyophilized compositions in “the Original Applications” (the '881 Application/'608 Publication, as well as the preceding '511 Provisional Application). (*See, e.g.*, Ex. 1015 at ¶ 204 (citing Ex. 1003 (file history of the '511 Provisional Application) and Ex. 1004 (file history of the '881 Application))). However, the '608 Publication also specifically discloses a crystalline form of the lyophilized phenobarbital sodium composition in addition to an amorphous lyophilized phenobarbital sodium composition. In particular, the '608 Publication states: “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%.” (Ex. 1005 at [0012] (emphasis added).) Dr. Suryanarayanan quoted this sentence but neglected to opine on what it would mean to a POSA. (Ex. 1015 at ¶ 213.)

138. In my opinion, a POSA reading this sentence at paragraph [0012] of the '608 Publication would understand that (1) a crystalline, lyophilized phenobarbital sodium composition is disclosed therein; (2) this crystalline lyophilized phenobarbital sodium composition can exist in a mixture with an amorphous form in any proportion quoted therein; and (3) the inventors stated a

preference for “the percentage of the lyophilized formulation that is amorphous” to be “at least 20%.” This paragraph [0012] thus specifically discloses to a POSA mixtures of both crystalline and amorphous types of “the lyophilized [phenobarbital sodium] formulation.”

139. Furthermore, in the “Original Applications,” and specifically in the Provisional Application (Ex. 1003) claim 17 recites:

17. A method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, the method comprising:

adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution;
if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and
lyophilizing the Phenobarbital Sodium solution *to form stable lyophilized Phenobarbital sodium.*

(Ex. 1003, the '551 Provisional Application at 27, claim 17 (emphasis added).)

140. As stated above, I am informed by counsel that a claim in a provisional application is legally considered part of the disclosure of that application for the purpose of determining priority of a later-filed related patent application. In claim 17 of the '551 Provisional Application, the “stable

lyophilized Phenobarbital sodium” is the result of the claimed method. It is not reciting a method step that involves the use of a particular bulk solution. Therefore, here is a clear disclosure of “stable lyophilized Phenobarbital sodium” without reference to its crystallinity or amorphicity in one of the Original Applications.

141. When the '608 Publication contrasts an amorphous lyophilized phenobarbital sodium composition with prior art disclosures of a crystalline material, none of that crystalline material was lyophilized. Dr. Suryanarayanan cited several of these comparisons (Ex. 1015 at ¶ 212) contrasting amorphous lyophilized compositions to: (1) “crystalline granules or crystals dissolved in an aqueous solvent,” which hence were no longer even in a solid form; (2) “crystalline material” in general, but *not* to a *lyophilized* crystalline material (see Ex. 1005 at [0011] (discussing a superior stability of a crystalline material as a general principle and citing to a corresponding general reference, but *not* discussing any crystalline *lyophilized* material)); (3) “USP grade phenobarbital in the prior art,” referring to the chemical sold by the Siegfried USA commercial company described in the '608 Publication, paragraph [0074], which is, again, *not* a lyophilized material; and (4) “the USP grade P API,” which is also *not* a lyophilized material. (Ex. 1015 at ¶ 212.) Therefore, a POSA reading these statements would have no reason to understand the inventors as disparaging

crystalline *lyophilized* phenobarbital sodium. In other words, these comparisons do not represent some sort of a selection, or exclusion, between crystalline lyophilized phenobarbital sodium and amorphous lyophilized phenobarbital sodium.

142. Dr. Suryanarayanan also cites to a declaration statement of one of the Nivagen named inventors, Dr. Dasaradhi Lakkaraju, made during the prosecution of the '881 Application. (Ex. 1015 at ¶ 214.) In that statement, Dr. Lakkaraju was clearly discussing amorphous and crystalline materials *in general*. In fact, the passage Dr. Suryanarayanan cites from Dr. Lakkaraju's declaration plainly states that "[b]ecause of that *general notion* [that amorphous forms 'would be *normally* considered as inferior to crystalline forms'], ..." (*Id.* (emphases added)). There is thus *no* comparison made specifically between amorphous and crystalline *lyophilized* phenobarbital sodium compositions.

143. Therefore, (1) because the '608 Publication clearly discloses to a POSA a crystalline lyophilized phenobarbital sodium composition (which "preferably" exist in a mixture with an amorphous lyophilized phenobarbital sodium composition in a wide range of proportions (Ex. 1005 at [0012])), and (2) because the '511 Provisional Application includes a claim that discloses a product of a lyophilization method that is "*stable lyophilized Phenobarbital sodium*" without restriction as to its crystallinity or lack thereof, a POSA reading these

Original Applications would find adequate written description support for all the claims of the '076 patent that are silent as to the crystallinity of the claimed storage-stable lyophilized phenobarbital sodium composition. Nothing in the '608 Publication or any other material Petitioner and Dr. Suryanarayanan asserted would change this understanding by a POSA, as discussed above.

144. I reserve the right to amend or supplement my opinions expressed in this Declaration based on the PTAB rules and in view of any claim construction positions that may be adopted by the PTAB, as well as any additional discovery, declarations, testimony, or arguments proffered by Sun Pharma later in these proceedings.

DATE: August 10, 2025

A handwritten signature in blue ink, appearing to read 'A. M. Klibanov', written over a horizontal line.

Alexander M. Klibanov, Ph.D.