

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, INC.,

Petitioner

v.

NIVAGEN PHARMACEUTICALS, INC.,

Patent Owner

IPR2025-00731
Patent No. 11,925,661

**DECLARATION OF BARRETT RABINOW, Ph.D. IN
SUPPORT OF PATENT OWNER'S PRELIMINARY
RESPONSE TO PETITION FOR *INTER PARTES* REVIEW**

I, Barrett Rabinow, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by Patent Owner Nivagen Pharmaceuticals, Inc. (“Nivagen”) as an independent expert consultant to render my opinions on technical issues within my knowledge and expertise. These issues relate to one or both of Petitioner Amneal Pharmaceuticals, Inc.’s (“Amneal”) challenges of U.S. Patent No. 11,813,291 (“the ’291 patent”) in IPR2025-00779 and U.S. Patent No. 11,925,661 (“the ’661 patent”) in IPR2025-00731.

2. I previously submitted a declaration in this IPR proceeding, as well as in the related IPR2025-00779, to explain what was the Phosphate Polyfusor® (“PPF”) product discussed in the “Terlevich” reference (Ex1009 in both of these Petitions), how it was used when it was available in the United Kingdom (it was never approved in the United States), and whether and how that product differed in important ways from a sterile, ready-to-use (RTU) potassium phosphate solution or injection product claimed in the ’291 patent or the ’661 patent. In my opinion, PPF was not a sterile, RTU product, and its drawbacks and potential dangers to the patients were well-known and well-published in the relevant field of art. I incorporate by reference my Declaration dated July 16, 2025 and filed as Exhibit 2006 by the Patent Owner in this IPR2025-00731.

3. I was also asked to address whether the application for the “parent” ’291 patent, which is U.S. Patent Application No. 17/499,001 (“the ’001 application”), when viewed from the perspective of a person of ordinary skill in the art, provides disclosure and support of a “1.5 mmol/100 mL to 15 mmol/100 mL phosphorous” concentration range found in the ’661 patent claims. In my opinion, it does.

II. QUALIFICATIONS

4. I am an expert in pharmaceutical research and development and sterile drug development. I have over 40 years of industrial chemistry experience. I am a named inventor on at least 15 granted U.S. patents, as well as additional applications and foreign patents.

5. During a litigation in the District of Delaware involving the ’291 patent and the ’661 patent, case number 24-846, which I understand is still ongoing, I served as an expert declarant in a preliminary injunction proceeding and rendered opinions relating to the same field of technology as my opinions here.

6. I currently am a consultant for the pharmaceutical industry. My consulting practice includes R&D, manufacturing, regulatory, quality, and patent issues, with an emphasis on sterile injectable dosage forms, and issues concerning chemical reactions, formulations, stability, reaction rates, leaching, gas

transmission through plastic, closure/container technology, impurities, and generally characterization and analysis of pharmaceutical products.

7. Further details of my qualifications were set forth in Part II of my Declaration dated July 16, 2025 and filed as Exhibit 2006 by the Patent Owner in IPR2025-00731, incorporated by reference here.

8. Other details concerning my background, academic work, and professional history are set forth in my curriculum vitae, which was filed as Exhibit 2007.

9. I am being compensated at my normal consulting rate for the time I spend on this matter. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

III. DOCUMENTS AND MATERIALS CONSIDERED

10. I have reviewed the two petitions for *inter partes* review Amneal filed with the Board, including the exhibits relevant to my opinions here, and in particular the “Nivagen-1” reference, which is U.S. Patent Application Publication No. 2022/0110969 and the published version of the ’001 Application, and the Declaration of Dr. Mansoor M. Amiji dated April 11, 2025 that were filed with Petition IPR2025-00731. Petitioner filed “Nivagen-1” as Ex1006 in both Petitions, and also referred to it as “the ’001 application” in the Petition. In the

litigation in the District of Delaware, Dr. Amiji and Petitioner also referred to this reference as “Pandya.” I will use “Nivagen-1” below.

11. I have also found and reviewed the additional publications and other publicly available information regarding phosphorus concentrations for injectable products. In forming my opinions, I also relied on my experience and my education.

IV. QUALIFICATION OF A PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

16. A POSA for the ’291 patent and the ’661 patent would have had at least a Ph.D. degree in chemistry or biochemistry 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, and development, optimization, and manufacture, including experience with processes and techniques for minimizing impurities in and improving the stability of, pharmaceutical drug products during manufacture and storage.

17. I have reviewed the POSA definition given by Dr. Amiji in his Declaration in support of Amneal’s petitions. (Ex. 1003 at ¶¶24-26). Dr. Amiji opined that “a POSITA would have had an advanced degree in chemistry, biology and/or pharmaceuticals, plus a few years (e.g., 2-3) of experience in *preparing parenteral formulations*. Additional education may serve as a substitute for a lack

of experience and vice versa.” (*Id.* at ¶26 (emphasis added by me)). I am not quite sure what Dr. Amiji meant by “preparing parenteral formulations.” If he meant activities relating to “pharmaceutical drug product formulation, analysis, and development, optimization, and manufacture, including experience with processes and techniques for minimizing impurities in and improving the stability of, pharmaceutical drug products during manufacture and storage,” as I set forth above but further limited to “parenteral formulations” which includes injectables like the claimed subject matter in the ’291 patent and the ’661 patent, I can accept Dr. Amiji’s definition. I do not believe Dr. Amiji’s definition of a POSA would change my opinions below.

V. THE ’001 APPLICATION PROVIDES WRITTEN SUPPORT FOR THE “1.5 TO 15 MMOL/100 ML PHOSPHOROUS” RANGE

A. “DAILY MAXIMUM” REQUIRES DOWNWARD ADJUSTMENT OF PHOPHOROUS CONCENTRATION FOR THE RTU PRODUCT

18. There is adequate written description in Nivagen-1 for the ’661 patent claims reciting 1.5 mmol/100 ml to 15 mmol/100 ml phosphorus.

19. Paragraphs 44 and 45 of Nivagen-1 state:

[0044] In preferred embodiments, the rate of infusion of the sterile RTU potassium phosphates in sodium chloride solution into the patient is selected from 6.8 mmol/hour or 15 mmol/hour. In typical embodiments, the sterile RTU potassium phosphates in sodium chloride solution is administered to an adult or pediatric patient 12 years of age and older by peripheral venous catheter at 6.8 mmol/hour. In more preferred embodiments, the concentration of

phosphates administered by peripheral venous catheter is not more than 6.8 mmol/100 ml in adult patients or pediatric patient 12 years of age and older and **not more than 2.7 mmol/100 ml** in pediatric patients less than 12 years of age.

[0045] In other typical embodiments, the sterile RTU potassium phosphates in sodium chloride solution is administered to an adult or pediatric patient 12 years of age and older by central venous catheter at 15 mmol/hour. In more preferred embodiments, the concentration of phosphates administered by central venous catheter is not more than 18 mmol/100 ml in adult patients or pediatric patient 12 years or age and older and **not more than 5.5 mmol/100 ml** in pediatric patients less than 12 years of age.

(Emphasis added by me).

20. A POSA reading these paragraphs would understand that “not more than 2.7 mmol/100 ml” or “not more than 5.5 mmol/100 ml” discloses that a phosphorus concentration as low as 1.5 mmol/100 ml is suitable for administration to pediatric patients less than 12 years of age. A POSA would further understand from this disclosure, and the disclosure that not more than 18 mmol/100 ml phosphorus is suitable for CVC administration in adult and older children, that a ready-to-use potassium phosphates product containing from 1.5 mmol/100 ml to 15 mmol/100 ml of phosphorus is suitable for administration to patients.

21. These lower concentrations of phosphorus (not more than 2.7 or not more than 5.5 mmol/100 ml) for use in pediatric patients less than 12 years of age, along with “not more than 6.8 mmol/100 mL” and “not more than 18 mmol/100 mL” for adults and older children, are also illustrated in Table 1 (part of

paragraph [0005]) in Nivagen-1, which sets forth “Maximum Recommended Daily Concentration of Potassium Phosphates Injection By Age and Route of Administration (Peripheral vs. Central)”:

TABLE 1

Patient Population	Peripheral Venous Catheter	Central Venous Catheter
Adults and Pediatric Patients (12 Years of Age and Older)	Phosphorus 6.8 mmol/100 mL (Potassium 10 mEq/100 mL)	Phosphorus 18 mmol/100 mL (Potassium 26.4 mEq/100 mL)
Pediatric Patients (Less than 12 Years of Age)	Phosphorus 0.27 mmol/10 mL (Potassium 0.4 mEq/10 mL)	Phosphorus 0.55 mmol/10 mL (Potassium 0.8 mEq/10 mL)

22. The introductory text for Table 1 is informative. It states:

[0005] Hypophosphatemia is a clinical condition in which serum phosphate concentrations are less than 2.5 mg/dL (0.81 mmol/L). ... In most cases, the treatment for hypophosphatemia is phosphorus replacement therapy with an intravenous (IV) infusion rate of phosphates that **must be adjusted to the patient’s age and particular need**. Phosphorus replacement therapy is generally administered via peripheral venous catheter or central venous catheter and at a rate according to the maximum recommended concentration and infusion rate as is shown in Table 1

(Emphasis added by me).

23. This disclosure tells a POSA that the infusion rate of an infusion product “must be adjusted to the patient’s age and particular need,” which, in the context of a disclosure of a “maximum recommended daily concentration and infusion rate as shown in Table 1,” must mean a *downward* adjustment from that maximum. That is the only reasonable reading of this passage by a POSA. The infusion rates in Table 1 are stated in a concentration format, as certain moles of

phosphorus *carried per 100 mL or 10 mL* of liquid, which fit the definition of a concentration (moles of nutrients in a certain volume). A POSA reading paragraph [0005] would understand that an RTU product containing 100 mL of liquid must contain an amount of nutrients adjusted from the daily maximum downwards, from 18, 6.8, 5.5, or 2.7, down to 1.5 mmol/100 mL or another concentration to accommodate “the patient’s age and particular need.”

24. Furthermore, paragraph [0005] of Nivagen-1 states that phosphorus replacement therapy is generally administered “at a rate according to the maximum recommended concentration and infusion rate,” which does not mean that the therapy must be carried out *at the maximum*. Rather, a POSA is instructed to find “a rate” *according to* the maximum, which a POSA would understand to mean “not to exceed the maximum,” because that is what the word “maximum” means. Again, the “rate” must be *adjusted* to be suitable for the patient’s age and particular need. When there is a maximum, the only adjustment that can be done is downwards.

25. In Petition IPR2025-00731, p. 10, Petitioner argues that:

Thus, a POSITA would *not* understand the “not more than” disclosures of ¶¶0044-45 to be a disclosure of the concentration of the sterile, RTU phosphate solutions themselves; instead, a POSITA would know that these disclosures relate to the *daily maximum* concentrations allowed for pediatric patients depending on whether the administration was via peripheral venous or central venous administration. (Ex-1003-Amiji at ¶¶145-148.).

I do not understand Petitioner’s reasoning. To a POSA reading Nivagen-1, the invention disclosed in the patent application is an RTU phosphate solution product addressing a patient’s need for additional phosphorus by infusion. The product contains a concentration of phosphates, which provide phosphorus, and that concentration in the product must be adjusted to address the patient’s “particular need.” The daily maximum sets a ceiling of how much phosphorus to administer, and a POSA is instructed to adjust the concentration and infusion rate downwards from the maximum, which supports a suitable range of concentration and infusion rate that encompasses 1.5 mmol/100 mL. Contrary to Petitioner’s and Dr. Amiji’s view, Nivagen-1 does not teach a POSA to administer phosphorus to a patient *at the daily maximum* regardless of the patient’s particular need. In fact, the teaching is just the opposite—the teaching is to make adjustment of the phosphorus concentration and do it in a 100 mL volume.

**B. A POSA CAN READILY ENVISION RTU PRODUCT
PHOSPHORUS CONCENTRATIONS DOWN TO 1.5
MMOL/100 ML**

26. Dr. Amiji opines that, “even if the above not more than disclosures did constitute a disclosure of phosphate concentrations for the sterile, RTU solutions (they do not), such disclosures still fail to disclose the claimed Phosphorous Range.” (Ex1003 at ¶149). Dr. Amiji argues that the disclosed range should go all the way down to “>0.” (*Id.*).

27. Dr. Amiji entirely missed how a POSA would determine “how low should the concentration go.” A POSA would consider the toxicity question in determining how much downward adjustment to do for an injectable product. Human and animal toxicology studies seek to determine the derived no-effect level, or “DNEL,” of the chemical under study. Once the DNEL is found from the study, it is customary to apply an intraspecies Assessment Factor, or “AF.” This effectively extrapolates the DNEL to the entire range of toxicological sensitivity encountered by the species, in this case human. The most sensitive individuals are typically children, particularly neonates:

The intraspecies variation in humans is greater than that in the more homogenous experimental animal population. For intraspecies extrapolation, the REACH TGD requires a default AF of 10 for the general population and of 5 for the more homogenous workforce, because the very young and very old are not part of this target population.¹

(Emphasis added).

28. This is explained in more detail in the same source:

Falk-Filipsson et al (2007) analysed data on the variations in

¹ Exhibit 2027, ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals, Guidance on Assessment Factors to Derive a DNEL. ECETOC Technical Report No. 10, Brussels, p. 30. Found at <https://www.ecetoc.org/wp-content/uploads/2021/10/ECETOC-TR-110-Guidance-on-assessment-factors-to-derive-a-DNEL.pdf>

sensibility available for neonates and young children and interpreted the publications as follows: - “A children’s pharmacokinetic database ... by Hattis et al” (1999a) “...indicated that premature and full-time neonates tend to have 3-9 times longer half-lives than adults” for drug clearance. “This difference disappears by 2-6 months of age..... As the range of neonate/adult half-life exceeds the default assessment factor of 3.2, this factor may not be adequate in the early postnatal period.” The factor of 3.2 was taken from IPCS (1994; 1999) that suggested subdividing the intraspecies AF of 10 evenly into 3.2 for both toxicokinetics and -dynamics.

Therefore, Falk-Filipsson and co-workers suggest an additional intraspecies AF of 1-10 for young children under the conditions also defined by the REACH TGD (see above). This proposal if related to neonates is also supported by ECETOC.

(Exhibit 2027, p. 31 (emphasis added)).

29. Accordingly, a POSA interested in determining a lower bound for “**not more than 2.7 mmol/100 ml** in pediatric patients less than 12 years of age”, would likely resort to the intraspecies variability factor of 10, detailed above, and divide an adult rate of 15 mmol/100ml by 10 to obtain 1.5 mmol/100ml.

30. This rule of thumb analysis is encouraged by the World Health Organization. In the following excerpts, the document defines the following abbreviations:

ADI acceptable daily intake

CSAF chemical-specific adjustment factor

HBGV health-based guidance value

POD point of departure

5.4.2 Uncertainty factors

In the past, the term “safety factor” rather than “uncertainty factor” was often used, particularly in the establishment of ADIs. The term “uncertainty factor” is now preferred. Comparable terms used by other bodies are “adjustment factor” and “assessment factor”, although some reserve the use of “adjustment factor” for data-derived factors. Application of the factors is intended to provide an adequate margin of safety for the consumer, considering sensitive human population subgroups, including infants (above 12 weeks of age) and young children.

Extrapolation is a necessary part of all risk assessments....

In the absence of quantitative species-specific toxicokinetic or toxicodynamic information on a particular substance, an overall default uncertainty factor of 100 is used to convert a POD from a study in experimental animals into an HBGV for human exposure (IPCS, 1999). The default 100-fold uncertainty factor represents the product of two separate 10-fold factors: a factor of 10 to cover interspecies differences between the experimental animal species and humans and a factor of 10 to cover intraspecies (interindividual) differences between humans. Each of the default factors of 10 takes into account differences in toxicodynamics (the effect of the chemical on the body) and in toxicokinetics (the fate of the chemical in the body). The interspecies uncertainty factor for toxicodynamics is designed to cover differences between the average responses in the experimental animals used in the study identified to derive the POD and those in average humans. The intraspecies (interindividual) uncertainty factor for toxicodynamics is designed to cover the differences in responses in humans between those who are least

sensitive to the substance and those who are the most sensitive.²

(Emphasis added).

31. Dr. Amiji raises several irrelevant issues regarding the range of concentrations specified in the patent. For example, “[t]he ’661 patent considers the phosphorus concentration *to be critical* such that even a 1-5% change in concentration is significant.” (Ex-1003-Amiji at ¶151, citing ’661 patent at 3:45-51 (maximum 1% change allowed), 8:55-62 (maximum 3% change allowed), Table 8, Item 9 (maximum 5% deviation from the target concentration of 4.65 mg/mL (15mmol/100 ml) allowed upon release).)

32. My response is that the low % concentration changes deemed critical by Dr. Amiji citing the ’661 patent at 3:45-51 (maximum 1% change allowed), 8:55-62 (maximum 3% change allowed) have to do with permissible changes *during storage or stability testing*. After a product is made, the changes in phosphorus concentration over time *must* be low to demonstrate that the

² Exhibit 2028, WHO. Chapter 5 Dose–response assessment and derivation of health-based guidance values, in EHC 240: Principles for Risk Assessment of Chemicals in Food, Second edition, 2020, pp. 5-46 to 5-47. Found at https://www.who.int/docs/default-source/food-safety/publications/chapter5-dose-response.pdf?sfvrsn=32edc2c6_5

formulation is in fact stable and does not change appreciably. As such, these windows of permissible *chemical* change have nothing to do with the intended concentrations of phosphorus used in a *medical* context for pediatric cases. Whatever the intended medically-oriented concentration is designated, which can be in a wide range depending on the patient's age and particular need, then the low % concentration changes deemed critical would be applied to ensure that the designated concentration is indeed present in the product following storage.

33. Both Dr. Amiji and Amneal referred to “Table 8, Item 9 (maximum 5% deviation from the target concentration of 4.65 mg/mL (15mmol/100 ml) allowed upon release).” (Ex-1003-Amiji at ¶151; Petition at 10-11). Both Dr. Amiji's opinion and Petitioner's argument completely missed the point. The “maximum 5% deviation from the target” requirement concerns the manufacture of a product with a designated concentration. It does not concern what the intended or labeled concentration range of the product can be. This disclosure refers to a standard quality parameter typically required to designate the permissible excursion of actual commercial product from the labeled concentration, as required by FDA and the USP. As such, these windows of permissible *quality* change have nothing to do with the intended concentration used in a *medical* context in pediatric cases. The 5% permissible deviation from target value would be applied to whatever the appropriate medically-derived

concentration is designated, such as between 1.5 mmol/100 mL (for younger children) and 15 mmol/100 mL (for adults and older children).

C. THE “1.5 TO 15 MMOL/100 ML PHOSPHOROUS” RANGE CAN BE READILY ENVISIONED BY A POSA

34. I have reviewed Ex2013, which is the Koneru patent, U.S. Patent No. 11,141,430 filed in 2020 and issued in 2021. This patent is from a similar timeframe to Nivagen-1, and reflects a POSA’s knowledge and understanding at that time. Dr. Amiji noted that the Koneru patent was analyzed by the patent examiner during the prosecution of the ’001 Application (Nivagen-1) as well as later on for the ’661 patent. (Exhibit 1003 at ¶¶42-43).

35. As Dr. Amiji noted, the Koneru patent disclosed a concentrate product with a phosphorus concentration of 1 mM/mL. (*Id.*). That is 100 mmol/100 mL, much more than the phosphorus concentrations in an RTU product. As I will note below, the *disclosures* in the Koneru patent actually contain a much wider range of the concentrate product, from 1 mM P/mL to “about 30 mM P/mL.” (Ex2013 at column 14, lines 56-57). A product with a concentration of phosphorus in that range disclosed in the Koneru patent must be diluted before use (i.e. administration to patients).

36. The Koneru patent teaches how much to dilute before use. The diluted preparations should contain concentrations of phosphorus similar to those found in an RTU product, because the whole point of an RTU product is to

eliminate the dilution step and other potential sources of undesirable variability and harmful contaminations before administration to patients.

37. The Koneru patent teaches that:

The phosphate salts compositions or solutions provided herein may be formulated in a variety of dosage forms. Suitable dosage forms include injectable formulations, or
45 oral formulations. In some embodiments, the injectable formulation may be for parenteral administration, e.g., intravenous, intramuscular, intrathecal, and the like. In further embodiments, the injectable formulation may be for intravenous administration. In still further embodiments, the
50 formulations are provided in an infusion container (a glass vial, or a polymeric container such as an infusion bag or a blow-fill-seal manufactured plastic container) of 50 mL, 100 mL, 200 mL, 250 mL, 500 mL, 1000 mL, 2000 mL, 3000 mL, or 5000 mL. For example, formulations in the said
55 containers are prepared by diluting any of the phosphate ion concentrations mentioned above, i.e., 1 mM P/mL to about 30 mM P/mL. Thus, the final concentrations of the phosphate ion may range from 1/5000 to 1/50; 2/5000 to 2/50; 3/5000 to 3/50; 4/5000 to 4/50; 5/5000 to 5/50; 6/5000 to
60 6/50; 7/5000 to 7/50; 8/5000 to 8/50; 9/5000 to 9/50; or 10/5000 to 10/50. The polymeric container may be made of polypropylene, PVC, and the like, or mixtures thereof and the like. Such polymeric containers are known in the art and are widely used in the infusion practice. The equipment to
65 manufacture the containers, and the equipment to fill such containers with the drug product are also known in the pharmaceutical arts.

(Ex2013 at column 14, lines 42-67).

38. A POSA with the knowledge from the prior art would readily envision a diluted concentration of 1.5 mmol/100 mL to 15 mmol/100 mL as suitable for administration to patients, for example from the disclosures above. For example, diluting 1 mL of “30 mM P/mL” of concentrate (“P” means phosphorus), which is the same concentration as 3,000 mmol/100 mL, to 2000 mL total volume would result in 1.5 mmol/100 mL of phosphorus concentration. If 1 mL of the 30 mM P/mL concentrate product is diluted to 200 mL total volume, that would result in 15 mmol/100 mL. The Koneru patent specifically disclosed using 200 mL or 2000 mL for the dilution process, and a POSA would understand that a range of the phosphorus concentrations resulting from the dilution process taught in the Koneru patent is acceptable for use in an RTU product, for direct administration to patients.

39. I reserve the right to amend or supplement my opinions in this Declaration based on the rules of the Patent Trial and Appeal Board, and in view of any claim construction positions that may be adopted by the Board, or any discovery, declarations, testimony, or arguments proffered by Amneal later in these proceedings.

Date: 3 August 2025

Signature: Barnett E Palino