

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 DANIEL NORWOOD, Ph.D. IN SUPPORT
OF PATENT OWNER'S PRELIMINARY RESPONSE**

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I, Daniel Norwood, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by Patent Owner Nivagen Pharmaceuticals, Inc. (“Nivagen”) as an independent expert consultant in this proceeding before the Patent Trial and Appeal Board (“PTAB” or “Board”). The issues and opinions herein relate to both of Petitioner Amneal Pharmaceuticals, Inc.’s (“Amneal”) challenges of U.S. Patent Nos. 11,813,291 (“the ’291 patent”) in IPR2025-00779 and 11,925,661 (“the ’661 patent”) in IPR2025-00731.

2. I am being compensated at my normal consulting rate for my work. I have no other interest in this proceeding. 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 proceeding.

3. I have been asked to consider the allegations made in the Petitions for *Inter Partes Review* of the ’291 and ’661 patents, the declarations of Dr. Amiji in support of the Petitions, the asserted prior art, and the expert declarations of Dr. Rabinow. My opinions are set forth below.

II. BACKGROUND AND QUALIFICATIONS

4. I have 35 years of experience in the pharmaceutical development and manufacturing industries, and 49 years of total experience in chemical analysis and various public health related areas including environmental sciences and clinical

laboratory research, along with my pharmaceutical experience. I am currently Principal Consultant at Feinberg Norwood and Associates Pharma Consulting with headquarters in Chapel Hill, North Carolina. In this role I offer consulting services to the pharmaceutical development and manufacturing industries in areas such as general pharmaceutical development, pharmaceutical packaging development, and manufacturing problem solving.

5. Prior to joining Feinberg Norwood and Associates Pharma Consulting, I was a Distinguished Research Fellow at Boehringer Ingelheim Pharmaceuticals, Inc., where I focused on packaging and delivery system characterization, trace level impurity identification and analysis, drug substance and drug product degradation chemistry, as well as other technical areas in pharmaceutical development and manufacturing. I have experience in projects involving analytical development, formulation development for many dosage form types (including parenterals and injectables) and chemical development.

6. I obtained my Bachelor of Science degree in Biochemistry from Virginia Polytechnic Institute and State University in 1976, a Master of Science in Public Health (Environmental Chemistry) from the University of North Carolina at Chapel Hill School of Public Health in 1981, and a Ph.D. in Environmental Chemistry from the University of North Carolina at Chapel Hill School of Public Health in 1985.

7. I have been the Chair of the Leachables and Extractables Working Group of the Product Quality Research Institute (PQRI) from 2001 until 2007 (when the work of that group was completed), and I have been a member of the PQRI Working Group on Leachables and Extractables in Parenteral Drug Products (PDP) since 2007. The PDP working group focused on parenteral (infusion) and injectable dosage form packaging development regulations and scientific best practices. I have been a member of the United States Pharmacopeia (USP) General Chapters – Packaging, Storage, and Distribution Expert Committee from 2010-2020.

8. I have received a number of awards from my peers and employers, including: the American Chemical Society Environmental Division Graduate Student Award in 1986; the American Water Works Association First Place Academic Achievement Award in 1987; the Glaxo CEO's Award in 1994; the Boehringer Ingelheim President's Award in 2007; the Product Quality Research Institute Excellence in Research Award in 2009; and, the USP Award for an Innovative Response to Public Health Challenges in 2013.

9. I currently have 46 peer reviewed scientific publications, 28 books and book chapters, 22 publications of other types (published reports, and non-peer reviewed articles) and 194 presentation citations (scientific and regulatory presentations, extended abstracts, posters and presented training courses).

III. DOCUMENTS AND MATERIALS CONSIDERED

10. I have reviewed the two petitions for *inter partes* review Amneal filed with the Board, including the Declarations of Dr. Mansoor M. Amiji dated April 11, 2025 that were filed with the two petitions in IPR2025-00779 and IPR2025-00731, and the exhibits relevant to my opinions here. I have also found and reviewed additional publications and other publicly available information pertinent to the issues discussed in this Declaration. In addition, I reviewed the declarations of Dr. Rabinow submitted in support of Nivagen's Request for Discretionary Denial and Patent Owner Preliminary Response. In forming my opinions, I also relied on my experience and my education.

IV. PERSON OF ORDINARY SKILL IN THE ART

16. I agree with Dr. Rabinow that 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 ¶¶24-28). 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 ¶28 (emphasis added)). I agree with Dr. Rabinow's view that, if by "preparing parenteral formulations" Dr. Amiji 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," Dr. Amiji's definition is acceptable provided that it is limited to "parenteral formulations" which includes injectables like the claimed subject matter in the '291 patent and the '661 patent. Regardless, Dr. Amiji's definition of a POSA would not change my opinions below.

V. PROPER CLAIM CONSTRUCTION

18. I understand that Dr. Amiji opines that "none of the claim terms requires a specific construction, and all will be given their plain and ordinary meaning." Ex. 1003 ¶132. I further understand that Nivagen also does not believe any of the claim terms require a specific construction.

19. I understand that the claims are to be interpreted according to how they are understood by one of ordinary skill in the art based on the claim language itself, the specification and the file history, which I understand is considered the “intrinsic evidence.” I have carefully reviewed and considered this intrinsic evidence.

VI. THE '661 PATENT

20. The '661 patent states that it generally relates to “compositions and methods for potassium phosphates solutions for injection, especially as it relates to such solutions with ultra-low concentrations of aluminum where the solutions are packaged in a ready-to-use container at volumes and concentrations suitable for direct administration to a patient.” Ex. 1001 at 1:10-16.

21. As I explain further below, it is my opinion that the invention claimed in the '661 patent improved upon existing technologies and solved an unmet need in formulating parenteral potassium phosphates solutions with reduced aluminum content where such solutions are in a ready-to-administer formulation suitable for phosphorus replacement therapy, and where such solutions have sufficient tonicity, sterility, and storage stability.

22. The potential advantages of RTU infusion products relative to conventional reconstituted admixtures are well established (van der Linden et al., “Ready-to-Use Injection Preparations versus Conventional Reconstituted Admixtures,” *Pharmacoeconomics* 2002, 20(8): 530 (Ex. 2029, “van der Linden”)).

These potential advantages include enhanced safety, convenience, better quality control, time savings (particularly in emergency situations), and lowered risk of harm to patients caused by errors made by medical personnel. To quote van der Linden, RTU systems were found to:

[F]acilitate[] efficiency, accuracy, and safety: efficiency as it streamlines IV work flow, creating more time for clinical activities and patient interaction, reduces steps in IV preparation, eliminates admixing labour, assembly and supplies and reduces waste by providing extended shelf-life over admixed solutions; accuracy as it reduces the risk of medication errors, eliminates calculations during compounding and guarantees accuracy in IV medication labelling; and safety as it facilitates immediate use in emergency situations, ensures sterility and potency with a closed system and eliminates the need for further product manipulations.

However, the actual pharmaceutical development process for any particular RTU infusion drug product, whether starting with an admixture or not, includes numerous challenges which make the actual development of an RTU product non-obvious.

23. Developing drugs generally is a long, expensive, and complex process with high uncertainty and a significant failure rate. Moreover, developing ready-to-use drugs presents a unique set of challenges compared to traditional drug development, including stability, sterility, compatibility, and regulatory hurdles. For example, RTU formulations must maintain their integrity throughout storage and

shelf-life, which can be challenging due to potential degradation pathways influenced by factors like temperature, humidity, and oxidation. Additionally, optimizing the solubility and bioavailability of drugs within RTU formulations is crucial for effective drug delivery and patient outcomes. Notably, for injectable RTU formulations, achieving the correct viscosity is essential for ease of administration and patient comfort. Also, the interaction between the active pharmaceutical ingredient and chosen excipients used in the formulation can lead to stability issues, affecting potency and shelf life. Furthermore, the packaging material itself must be compatible with the drug formulation to prevent leaching or interaction that could compromise the drug's stability or efficacy. Importantly, too, maintaining sterility throughout the entire RTU drug manufacturing process, from raw materials to final packaging, is crucial and requires rigorous validation of sterilization methods. In sum, developing RTU drugs requires a multifaceted approach to address the combined challenges of stability, sterility, manufacturing, regulatory compliance, and formulation specifics to ensure safe and effective patient care.

24. These major challenges require significant experimental work measured in years, and include: chemical stability of the formulation, physical stability of the formulation, compatibility of the formulation with the packaging system, characterization of potential impurities from the packaging system

(“leachables”), establishment of an adequate shelf-life, sterilization and aseptic processing, and development of robust quality control systems. Indeed, such tests are required by regulatory authorities including the FDA. Moreover, regulatory bodies, like the FDA, have strict requirements for RTU drugs to ensure their safety, efficacy, and sterility. These can be lengthy and complex, potentially delaying market access. And, even after approval, RTU drugs are subject to ongoing monitoring for safety and efficacy, requiring post-marketing studies and reporting of any adverse events.

VII. PRIMARY REFERENCES RELIED ON BY PETITIONER

A. Nivagen-1

25. Nivagen-1 is U.S. Patent App. Pub. No. 2022/0110969, filed as the '001 application, and published April 14, 2022. Ex-1006, Cover. Dr. Amiji relies on Nivagen-1 only with respect to Ground 1, arguing that Nivagen-1 anticipates the challenged claims.

26. I understand that Dr. Rabinow is offering opinions with respect to Dr. Amiji's arguments concerning Ground 1 and Nivagen-1 and I do not offer any further opinions here. If asked, I may do so in the future and reserve all rights to address the issue if needed.

B. The CMP Art

27. I understand that the CMP Art consists of two related references originating from CMP Development LLC (“CMP”), *i.e.*, International Patent Application Publication No. WO2020/081118 (the “CMP-PCT”) (Ex. 1007) and the FDA drug label related to the same composition (the “CMP-FDA”) (Ex. 1008).

28. Notably—and as admitted by Dr. Amiji—the CMP Art is not a ready to use formulation. Dr. Amiji readily concedes, as he must, that “CMP-PCT’s solutions are diluted ‘with a pharmaceutically acceptable diluent to obtain a diluted composition,’ which diluted solutions are then intravenously administered to the patient.” Ex. 1003 at ¶199 (quoting CMP-PCT at 4:25-27).

29. Dr. Amiji then goes on to posit that “[n]onetheless, it was obvious to produce (premix) and ship the CMP-PCT solutions as ready-to-use solutions.” *Id.* I strongly disagree. Dr. Amiji minimizes what a formulator would need to consider and account for. This is not a simple matter of taking a concentrated solution and diluting it and placing it into a container. A POSA would never do anything of the sort as it would risk accuracy of the formulation, stability, sterility and other factors which would compromise the aforementioned advantages of an RTU drug product.

30. As explained above, there are numerous challenges in formulating ready-to-use solutions. It is not obvious to start with a concentrated solution that requires dilution prior to administration and simply dilute it and place it in an IV

bag. As I explain further below, numerous parameters and variables need to be extensively tested at every step.

31. As concerns the CMP drug label that Dr. Amiji refers to as CMP-FDA, it is my opinion that this reference is not prior art. I understand that in order to constitute prior art, it must be accessible to the public before the effective filing date of the patent application, *i.e.*, the information must be disclosed in a way that someone skilled in the relevant field could have reasonably discovered it. Dr. Amiji suggests that CMP-FDA may have been “published no later than September 23, 2019” simply because a current FDA statement indicates that FDA updates information about approved drugs within two days of approval. Ex. 1003 at ¶¶93-95. But this post is not from 2019 and nothing in FDA’s statement indicates that FDA will publish the labeling within two days after a drug is approved.

32. Dr. Amiji also opines that the CMP FDA drug label was published on September 23, 2020 and he relies on an internet archive (Ex. 1027). In my opinion, it is not clear that the CMP FDA drug label actually was disclosed in a way such that someone skilled in the relevant field could have reasonably discovered it.

C. Terlevich

33. I understand that Dr. Rabinow previously submitted an expert declaration in support of Nivagen’s Request for Discretionary Denial and offered several opinions concerning the Terlevich reference (Ex. 1009), which describes

Fresenius Kabi's Phosphates Polyfusor® or "PPF" product. I read Dr. Rabinow's declaration and I agree with his opinions therein.

34. Specifically, I agree that there is no disclosure concerning whether or how a PPF container is to be prepared prior to infusion, and I further agree that the PPF is *not* a sterile, ready-to-use product. Instead, it is a "semi-rigid" container that must be vented externally to allow air to enter and the fluid to egress. Such an opening that is necessarily present on a semi-rigid container for infusion allows contamination. The drug product described in Terlevich requires a preparatory step of opening or generating the vent before use, which is the opposite of the sterile, ready-to-use drug product.

35. Notably, too, the PPF turned out to be detrimental to patients and was never approved for use in the United States. It was used by the National Health Services in the United Kingdom for a few years, but I understand that it was discontinued in early 2020.

36. In my opinion, and as I explain in detail below, a POSA would neither turn to Terlevich given the significant problems with such a device, nor would a POSA be motivated to combine Terlevich with the CMP Art with any reasonable expectation of success.

D. Ogawa

37. Dr. Amiji “optionally” cites to Ogawa for the proposition that Ogawa purportedly would have provided motivation to keep aluminum levels to 50 ppb or less so as to endeavor to eliminate aluminum-phosphate particles in intravenous solutions. Ex. 1003 at ¶¶222-223.

38. I am not sure why Dr. Amiji “optionally” cites Ogawa but in any event, it is my opinion that a POSA would not have found Ogawa to be pertinent. Ogawa simply discusses the effects on particle formation from glass vials containing certain buffering solutions. The purpose of Ogawa was to study the corrosive effects on glass surfaces and particles formed as a result of interaction between the inner surface of glass and certain drug productions. Ex. 1010 at p. 8. Ogawa noted that phosphate buffers may be used in injectables and studied the use of mixing a phosphate buffer and aluminum chloride for adjuvants in vaccines. Ex. 1010.

39. A POSA would not have considered Ogawa at least because (1) a POSA would not have used a glass container for a ready-to-use formulation and (2) Ogawa’s studies concerning phosphate buffers in glass containers for vaccines would not have been considered relevant.

E. Nevakar

40. Dr. Amiji relies on Nevakar only in Ground 3. According to Dr. Amiji, “[t]he Ground 1 art teaches most claim limitations except those relating to flexible

containers and applying a secondary metallized overwrap to such containers” and opines that “it was obvious to package the RTU solutions taught by the Ground 2 art using the packaging teachings of Nevakar.” Ex. 1003 at ¶306. I disagree with Dr. Amiji’s analysis of what the Ground 1 art discloses as discussed above. I also disagree with Dr. Amiji that Nevakar would have taught a POSA the use of flexible containers for use with ready-to-use solutions.

41. Nevakar generally purports to relate to antioxidant-free, sterilizable epinephrine compositions with improved stability and a pH of 3.0-4.7. Ex. 1011 at [0010]-[0011]. While I agree with Dr. Amiji that Nevakar “contemplates” that the epinephrine compositions could be placed in “polymeric containers [that] may have a volume of between 100 mL and 1,000 mL, and may be further enclosed in a metallized over-container” (*Id.* at [0015]), I disagree with Dr. Amiji’s conclusion that a POSA would have been motivated to use the containers described by Nevakar with the solutions disclosed in the Ground 1 art with any reasonable expectation of success.

42. In my opinion, it would not have been obvious to a POSA reading Nevakar to specifically use the containers claimed in the ’661 patent. As discussed above, there are multiple factors that determine the appropriate type of container and volume and each factor would require extensive tests.

VIII. PETITIONER HAS NOT SHOWN A REASONABLE LIKELIHOOD OF PREVAILING ON AT LEAST ONE CLAIM

A. A POSA Would Not Have Been Motivated to Combine the Prior Art with a Reasonable Expectation of Success

1. There Is No Motivation to Combine the Prior Art

43. As a person of ordinary skill in the art, I would not look to combine the CMP Art (art that is neither ready to use nor sterile once it is diluted) with Terlevich (a device that is also not RTU and, when in use, is unsterile, was not FDA-approved and was quickly discontinued) and with Nevakar (an article concerning epinephrine compositions), optionally also with Ogawa (an article related to particle formation from glass vials for vaccines) to solve the problems of formulating potassium phosphates solutions in a sterile, ready-to-administer formulation with low aluminum that is suitable for phosphorus replacement therapy, and where such solutions have sufficient tonicity and storage stability.

44. In my opinion, Dr. Amiji plucks disparate references that, according to him, disclose a particular aspect of the claimed invention and cobbles them together. He uses a compilation of literature and other sources and simply assumes that the compilation would work. In my opinion, Dr. Amiji uses hindsight. He selectively gathers and combines different prior art references to create a mosaic that, according to him, resembles the patented invention, when in reality, there would have been no

reason or motivation at the time to combine those specific references in that particular way.

45. For example, Dr. Amiji relies heavily on CMP Art but, as he recognizes, that is neither a ready-to-use nor sterile formulation. It is undisputed that the CMP Art is not ready-to-use as it must be diluted and placed in an appropriate bag prior to use. Additionally, a POSA would understand that the diluted product might not be sterile because it may be rendered non-sterile by the process of removing the concentrate from the vial and mixing it with saline in another container. Such diluted solutions are typically only usable for a short period of time and may form particulate matter or discoloration upon dilution and prior to administration, indicating they are not sterile.

46. Furthermore, the CMP-PCT—Dr. Amiji’s primary reference—was concerned about adjusting amounts of monobasic potassium phosphate (“KMP”) and dibasic potassium phosphate (“KDP”) in solution as well as aluminum content due to storage in glass vials. Ex. 1007 at 1:14-28. These issues are not relevant to the challenged claims and a POSA would not have considered the CMP Art in the first instance. Notably too, the CMP-PCT highlights the challenges in formulating pharmaceuticals and many tests that need to be done to arrive at a suitable formulation. For example, the CMP-PCT prepared six test formulations having varying KMP and KDP concentrations and pH values, all of which were stored in

glass vials. The test formulations were evaluated after just twelve weeks of storage at various conditions. Ex. 1007 at 12:18-14:29.

47. The inventors were not satisfied with those tests because of the assumption that the KDP levels may be too high and storage conditions may not have been controlled. Ex. 1007 at 14:1-5. The inventors therefore prepared six additional test formulations that varied the amounts of KMP and KDP and then subjected them to the temperature of -15 degrees Celsius until they froze and then they were allowed to thaw by storing them at room temperature. Ex. 1007 at 14:8-25. Once the formulations reached room temperature, they were stored at 5 degrees Celsius.

48. Upon the conclusion of these tests, the inventors arrived at a preferred KMP/KDP concentrations and attempted to formulate it, but in doing so, they encountered issues including solubility, total potassium concentration, varying pH, and selection of an appropriate container. Ex. 1007 at 16:13-18:32. Once the inventors arrived at a final test formulation, they were stored for 18 months at varying temperatures. The only set of storage conditions that proved satisfactory was storage at 4-8 degrees Celsius for 18 months. *Id.* at 19:1-5.

49. But perhaps most importantly, a POSA would not have thought that any of the data and disclosures in the CMP Art could be extrapolated to developing

a ready-to-use formulation as claimed. It is not so easy as Dr. Amiji suggests to develop a ready-to-use product.

50. Indeed, the only reference that Dr. Amiji contends discloses a ready-to-use product—the Terlevich reference—shows that it was not so easy to develop a sterile, ready-to-use potassium phosphates in sodium chloride solution. Dr. Amiji plainly recognizes that the CMP Art that he starts with is clearly not ready-to-use because it has to be diluted (among other things) prior to use and he opines that just because the Terlevich reference does that step, it is ready-to-use. The problem with this theory is that the POSA would not arrive at a RTU product, they would arrive at a semi-rigid container that is not RTU.

51. Dr. Amiji relies on Terlevich for the proposition that “it was obvious to produce (premix) and ship the CMP-PCT solutions as ready-to-use solutions.” Ex. 1003 at ¶199. I disagree for several reasons.

52. **First**, the PPF system disclosed in Terlevich is not ready-to-use. As mentioned, I read the declaration of Dr. Rabinow and I agree with his opinions that, with the Terlevich PPF, the user first needs to open the valve and put the system in contact with air, which serves as driving force. The semi-rigid container for the PPF product requires an opening that connects the contents of that container to the outside air, for pressure equalization as the fluid volume drained out. Such a semi-

rigid plastic container must be vented externally to allow air to enter and the fluid to egress.

53. **Second**, the PPF system disclosed in Terlevich is not sterile. As noted, the user has to expose the formulation to air in order to inject it into the patient. Air carries with it significant contaminants, especially in a hospital, and can be deadly to the already vulnerable patients being treated. Indeed, the PPF system was never FDA-approved and was not a valid option in the U.S. In my opinion, this would motivate a POSA to turn away from the reference and not consider it at all.

54. **Third**, I disagree with Dr. Amiji that Terlevich's disclosure of a "semi-rigid cylindrical polyethylene container" would have motivated a POSA to select a polyolefin or polymeric container. There are numerous options for containers and it is not obvious to select a polyolefin or polymeric container. One would need to conduct extensive stability/compatibility studies to inform what type of container is best suited for the desired formulation, stability over the intended product shelf-life, and use. Indeed the '661 patent is replete with studies showing the extensive tests needed to evaluate potential containers (*see, e.g.*, Ex. 1001 at Table 20) and, as noted above, even the CMP-PCT conducted tests to evaluate containers.

55. Dr. Amiji also opines that "[a] RTU solution also helps avoid unnecessary calculations, and potential errors, by practitioners." Ex. 1003 at ¶204. While I do not necessarily disagree with this general statement, it does depend on

the circumstances. For example, larger hospitals have pharmacies with significant expertise in diluting IVs and are able to precisely verify the infusion bags they make. Additionally, smaller pharmacies may not have storage space for RTUs. It is very important to have a choice in my opinion, and, for support, I refer again to the van der Linden article (Ex. 2029) referenced earlier.

56. I also disagree with Dr. Amiji's opinion that it would be obvious to make the CMP-PCT solutions as RTU solutions at any concentrations while keeping the ratios of KMP and KDP the same. Ex. 1003 at ¶207. Once again, Dr. Amiji ignores the many factors and experiments that would affect the precise formulation chosen.

57. One example of Dr. Amiji's hindsight bias is clearly depicted in paragraph 208 of his declaration where Dr Amiji states:

CMP-PCT discloses a total phosphate concentration of 3 mmol/ml or 300 mmol/100 ml, which is 30 times higher than the 10 mmol/100 ml phosphate concentration of Terlevich's RTU solutions. (Ex-1007 at 2:29-32; Ex-1009 at 1326.) A POSITA would, therefore, find it obvious to decrease the KMP and KDP levels in the CMP-PCT solutions by a factor of 30 when preparing RTU solutions.

Ex. 1003 at ¶208. Dr. Amiji goes on to state that "[a] POSITA would not expect any change in particulate levels when diluting the CMP-PCT solutions by a factor of 30."

58. I disagree with Dr. Amiji on these points. As noted above, a POSA would not have made any assumptions but rather would have to conduct tests and experiments to ensure a proper formulation and patient safety, as required by regulatory authorities including the FDA. In my opinion, Dr. Amiji is using hindsight. He uses the challenged claims as a roadmap to select references and jump to conclusions about what the prior art would have achieved or taught to a POSA. A POSA would not assume that diluting by 30 would not cause the particulate levels to change. Indeed a POSA would not make any assumptions concerning critical parameters that relate to patient safety. A POSA would have to conduct extensive tests and set parameters. In my opinion, there is nothing but hindsight as to why Dr. Amiji randomly picks to dilute by 30.

59. A POSA would gather all the clinical evidence about phosphates required to treat patients and use that to select a reasonable concentration of phosphates so that clinically appropriate infusion rates could be used to achieve the individual patient's needs.

60. On this point, it bears emphasizing that, in his declaration concerning the challenged claims of the related '291 patent, Dr. Amiji makes the exact same assumption as to what factor a POSA would dilute to, but there he arbitrarily picks a factor of 20. Now, here, he picks 30. It is clear that Dr. Amiji is simply using hindsight to pick arbitrary disclosures and arrive at the claims. But this does not

make the claims obvious. As noted above, due to the many challenges in formulating RTU injectables, a POSA would not have arrived at the claims with a reasonable expectation of success without undue experimentation.

61. Dr. Amiji's reliance on Ogawa concerning low aluminum content similarly reflects hindsight bias. Ex. 1003, ¶222-224. A POSA seeking to solve the problem addressed by the claimed invention would not have considered Ogawa in the first instance because Ogawa concerns glass vials and a POSA would not have considered using glass as an RTU bag. Just because a POSA may think they can reduce the aluminum concentration in an RTU product, does not mean that the POSA could arrive at the claimed number.

62. In Ground 3, Dr. Amiji relies on Nevakar as disclosing "flexible bags suited for use with ready-to-use solutions, which may include a secondary metallized overwrap." Ex. 1003 ¶309. But Nevakar relates to epinephrine compositions in containers having a volume of between 100 mL and 1,000 mL. Dr. Amiji provides no sound reasons why a POSA would turn to Nevakar or combine it with the other Ground 1 prior art.

63. Indeed, Dr. Amiji's basis as to why a POSA would combine Nevakar with the Ground 2 art is that Nevakar describes that its containers are purportedly "well-suited" for use with and for storing ready-to-use solutions and purportedly help to maintain stability of such solutions. Ex. 1003 at ¶310. As discussed above,

however, a POSA would not have simply selected a container because it was used for an epinephrine product when that product, its formulation, pH requirements, sterility requirements, stability requirements, and storage conditions all are different from the novel formulation being invented. A POSA would have needed to test that container, along with many others, to arrive at a suitable choice, which is exactly what the inventors of the challenged patent did.

64. If it were so easy to arrive at the claims of the challenged patent, someone would have done it long ago, but they did not. Indeed, the challenged patent has already been shown to be novel and successful. I understand that, in a related District Court proceeding, the Court awarded a preliminary injunction and set the bond at approximately \$30 Million.

65. For all of the above reasons, it is my opinion that a POSA would not have been motivated to select the prior art relied upon by Dr. Amiji.

2. There Is No Reasonable Expectation of Success Without Undue Experimentation

66. Even if the multiple prior art references relied upon by Dr. Amiji did disclose the elements that are missing—which they do not— as a person of ordinary skill in the art, it is my opinion that there could be no reasonable expectation of success in combining them to come up with the invention disclosed in the challenged patent at least because the prior art combination still would not be sterile *and* ready-to-use *and* contain the precise formulation *and* stability that is recited in the claims.

67. In my opinion, the '661 patent solved an important problem in a meaningful way that required extensive work and testing to achieve. The claims recited in the '661 patent are precise. The '661 patent plainly lays out that the inventors conducted numerous experiments and complex calculations to arrive at the sterile, ready-to-use solutions recited in the claims. Specifically, as expressly disclosed in the '661 patent, the inventors conducted extensive tests, including stability studies, to determine the optimal formulation to be used. *See, e.g.*, Ex. 1001 at 10:1-28:67.

68. In my opinion, a skilled artisan could not take the potassium phosphates and sodium chloride (and other components) solution in the CMP Art, dilute it, put it in a flexible plastic bag and make it into an isotonic, sterile, stable, ready-to-use aqueous formulation recited in the claims. There is no reasonable expectation of success given all the parameters and testing that would be required as I describe above.

69. Moreover, transmuting the extant vial potassium phosphates solution into pre-mixed bags carries increased risks for chemical stability issues and physical stability issues, not only during the autoclaving process, but also during the storage period at room temperature afterwards. This is at least because, from a chemical standpoint, dilution has multiple potential risks, including a high risk for potential serious instability. Stability indicating variables may include changes in pH, ingress

of impurities from the packaging, increased lack of compatibility with the packaging, etc. This is among the reasons why testing needs to be done. Additionally, alterations in the packaging material, especially for solutions, may significantly increase the risk. This, combined with sterilization issues, raises potential problems for a formulator.

70. To this end, it bears noting that drug companies spend billions of dollars in developing drugs. This is because numerous examples fail during the extensive testing process. There are many failed attempts that only testing will reveal. Many of these failed attempts may have also been considered obvious under Dr. Amiji's analysis.

71. Thus, as one of ordinary skill, I would not have been able to make the asserted combination consistent with the teachings of the '291 patent without significant, undue experimentation.

B. The Challenged Claims are Not Unpatentable Over the Prior Art in Ground 2

Claim 1: A sterile ready-to-use aqueous potassium solution, comprising potassium phosphates and sodium chloride, wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous and equal or less than 50 mcg/L aluminum, and wherein the solution has a pH of between 6.2 and 6.8.

72. Dr. Amiji opines that the CMP Art in view of Terlevich teaches “a sterile ready-to-use aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride, wherein the solution comprises between 1.5

mmol/100 mL and 15 mmol/100 ml phosphorus” (Ex. 1003 at ¶¶228-234), that CMP-PCT (optionally in view of Ogawa) teaches “equal or less than 50 mcg/L aluminum” (Ex. 1003 at ¶¶237-241), and that CMP-PCT teaches “wherein the solution has a pH of between 6.2 and 6.8.” (Ex. 1003 at ¶¶244). I disagree.

73. First, as explained above, neither the CMP Art nor Terlevich teach or disclose “a sterile ready-to-use aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride” as required by claim 1. The solutions in the CMP Art and Terlevich are not ready-to-use and, to the extent they are prepared for administration, they are not sterile ready-to-use formulations. That is, the CMP Art needs to be diluted, a process that can easily compromise sterility, as even Dr. Amiji admits (e.g., Ex. 1003 at ¶199). And, as mentioned above, Terlevich significantly compromises sterility by exposing the formulation to outside air, which carries with it contaminants.

74. Additionally, it would not have been obvious to use sodium chloride as a tonicity agent. The CMP-PCT did not do so and, to the extent that Dr. Amiji relies on the CMP-FDA label (which as I noted above is not prior art) as disclosing this limitation (e.g., Ex. 1003 at ¶¶218-219), this does not make the claim limitation obvious as it would require extensive testing and evaluation to determine which tonicity agent to use.

75. I also disagree with Dr. Amiji that the CMP-PCT in view of Terlevich teaches the claim limitation “wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus.” Dr. Amiji concedes that neither CMP-PCT nor Terlevich disclose the claimed phosphorous concentration and opines that a POSA reading CMP-PCT and Terlevich would assume it would work to dilute by a factor of 30. Ex. 1003 at ¶234. For the reasons I explained above, a POSA would not draw such assumptions and would not combine prior art in this fashion. Instead, a POSA would consider the many differences between the CMP-PCT and Terlevich and would run numerous tests to determine the ideal phosphorous concentration. As I discussed above, there are numerous complications in developing RTU formulations. A POSA would not make the assumptions that Dr. Amiji is making but rather would conduct tests to ensure that the formulation is viable.

76. I also disagree that the CMP-PCT alone or “optionally” in view of Ogawa teaches to use equal or less than 50 mcg/L aluminum. Ex. 1003 at ¶¶238-242. The CMP-PCT merely states that “tests conducted in a plastic vial . . . shows an aluminum content of not more than about 5 ppm (viz., about 0.2 to about 0.3 ppm) after storage at 60°C at 60% relative humidity for 0.5- and 1.0-months.” Ex. 1007 at 19:19-26. Dr. Amiji does not explain how such a statement teaches or suggests the claimed range of aluminum and I do not believe it would have motivated a POSA to achieve the claimed range with a reasonable expectation of

success. Moreover, Ogawa is not related to ready-to-use formulations much less formulations for phosphorus replacement therapy and therefore adds nothing.

77. Dr. Amiji opines that the CMP-PCT alone teaches the pH limitation of this claim because it teaches its solutions have pH of about 6.5 to about 7.5. Ex. 1003 at ¶¶243-244. There are many significant distinctions between the formulation disclosed in the CMP-PCT and that of the claims, however, that would affect pH. For example, the CMP-PCT is not diluted and is not RTU. Additionally, the CMP-PCT did not use sodium chloride; it used dextrose. A POSA could not be sure that these types of changes would not affect the pH without extensive testing.

Claim 2: The solution of claim 1, wherein the potassium phosphates comprise potassium dihydrogen phosphate and potassium hydrogen phosphate at a molar ratio of about 0.7 to 1.3

78. Dr. Amiji opines that CMP-PCT in view of Terlevich teaches this limitation because “[t]he molar ratio of KDP:KMP in this solution is 1.34.” Ex. 1003 at ¶247. I disagree that a molar ratio of 1.34 makes the claimed molar ratio obvious given that it exceeds the claimed molar ratio and, in any event, a POSA would have expected materially different properties between the CMP-PCT solution, the Terlevich solution and the claimed solution. A POSA would not expect a molar ratio in a concentrated solution to necessarily stay the same after the solution is diluted.

Claim 3: The solution of claim 2, wherein the potassium dihydrogen phosphate is present in the solution an amount of between about 112 mg/100 ml and about 1,120 mg/100 ml and wherein the potassium hydrogen phosphate is present in

the solution in an amount of between about 118 mg/100 ml and about 1,180 mg/100 ml

79. I also disagree with Dr. Amiji that CMP-PCT in view of Terlevich teaches this limitation. Ex. 1003 at ¶¶250-251. As I explained above and also below with respect to claim 4, I disagree with Dr. Amiji's opinion that a POSA would have found it obvious based on these prior art references to dilute by a factor of 30.

Claim 4: The solution of claim 1, wherein the potassium is present in the solution in an amount of no more than 22 mEq/100 mL

80. Dr. Amiji opines that the CMP-PCT in view of Terlevich teaches this claim. Ex. 1003 at ¶¶253-255. I disagree. The CMP-PCT contains 470 mEq per 100 mL potassium. Ex. 1007 at 17:1-8. Dr. Amiji posits that it was somehow obvious to dilute the CMP-PCT solution by a factor of 30.

81. CMP-PCT was not a ready-to-use formulations as claimed in the challenged patent. There are many variables that affect the development of a suitable RTU formulation, as I discussed in detail above. Even if the CMP-PCT could somehow be combined with Terlevich to disclose to a POSA that the potassium in an RTU solution should be in an amount of no more than 22 mEq/100 mL—and they do not—the POSA would not make any assumptions but instead would have to undertake extensive testing to ensure, for example, stability, pH, and other factors.

Claim 5: The solution of claim 1, wherein the sodium chloride is present in the solution in an amount of up to 900 mg/100 ml

82. I also disagree with Dr. Amiji that the CMP Art in view of Terlevich renders this claim obvious. Ex. 1003 at ¶257. While the prior art may have mentioned the use of 0.9% saline, those solutions were not similar to the claimed solutions and a POSA would not simply assume that this saline concentration would work. There can be no reasonable expectation of success without having conducted extensive tests.

Claim 6: The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a total liquid particle count of no more than 360 and no more than 30 for particles having a size of equal to or greater than 15 and equal to or greater than 25 micrometer size, respectively.

83. Dr. Amiji relies on CMP-PCT in view of Terlevich as disclosing this claim. Ex. 1003 at ¶¶260-265. But the CMP-PCT only states that the composition has no visible particles after storage at either (1) 4-8°C for 3-months to 96-months or (2) 25°C and 60% relative humidity for 3-months to 24-months, or longer. Ex. 1007 at 3:13-21. The CMP does not disclose any particle count of a diluted solution placed in a flexible container after the steps recited in claim 6.

84. Dr. Amiji appears to recognize this defect and opines that “[a] POSITA also would have expected the CMP-PCT solutions to remain stable/particle-free when stored for 3-months or more in a suitable pharmaceutical grade RTU plastic container, such as Terlevich’s RTU container.” Ex. 1003 at ¶262. He bases this assumption on the ground that Terlevich’s semi-rigid containers were known and

conventional. I do not understand how the fact that such container may have been known or conventional would mean that they wouldn't affect stability, including particle counts. In my opinion, a POSA would not have extrapolated the disclosure in the CMP-PCT as being applicable to a diluted, RTU formulation placed in a flexible container. The CMP-PCT therefore does not render this claim obvious in my opinion.

Claim 7: The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in phosphorus of no more than 1% absolute.

Claim 8: The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in potassium of no more than 2% absolute.

85. Dr. Amiji opines that CMP-PCT in view of Terlevich teaches these claims and makes arguments similar to those with respect to claim 6. Ex. 1003 at ¶¶268-271. For the reasons I explained above with respect to claim 6, I disagree with Dr. Amiji's opinions that claims 7 and 8 would have been obvious over CMP-PCT in view of Terlevich. As I explained above, there are many differences between the prior art formulations and packaging versus those recited in the claims that could affect not only particle formation but also the change in phosphorus and potassium concentrations over time. A POSA would not simply assume that any stability disclosure in the CMP-PCT, Terlevich would apply to the RTU formulation claimed.

Claim 11: A sterile ready-to-use premixed pharmaceutical product stored in a flexible polymeric container, wherein the pharmaceutical product comprises a potassium phosphates in an aqueous sodium chloride solution containing (a) less than 50 mcg/L aluminum, (b) between about 1.5 mmol 100 ml and 15 mmol/100 ml phosphorus, and (c) about 22 mEq/100 mL potassium.

86. Dr. Amiji does asserts that “[a] POSITA would recognize semi-rigid polyethylene containers are ‘flexible polymeric containers’ because (a) they are made of polyethylene, which was known to be flexible, and (b) are ‘semirigid,’ i.e., have some flexibility, otherwise the author would have not used the word ‘semi-’ with the word ‘rigid.’” In my opinion, a POSA would not rely on such wordsmithing but rather would have known very well that Terlevich’s semi-rigid container has significant shortcomings including that it necessarily must be exposed to air when used. A POSA would not simply start with the CMP Art formulation, dilute it, and place it in Terlevich’s container to arrive at the claims for all the reasons I have explained herein.

87. Dr. Amiji’s remaining opinions for claim 11 all rely on his analysis above and I, too, rely on my analysis above for the remaining limitations of this claim.

Claim 12: The pharmaceutical product of claim 11, wherein the potassium phosphates comprise potassium dihydrogen phosphate and potassium hydrogen phosphate at a molar ratio of about 0.7 to 1.3, and/or wherein the potassium dihydrogen phosphate is present in the solution an amount of between about 112 mg/100 ml and about 1,120 mg/100 ml and wherein the potassium hydrogen phosphate is present in the solution in an amount of between about 118 mg/100 ml and about 1,180 mg/100 ml.

88. Dr. Amiji relies on his arguments concerning the claims 2-3 for claim 12. Ex. 1003 ¶¶281-282. I also rely on my opinions above for this claim.

Claim 13: The pharmaceutical product of claim 12, wherein the sodium chloride is present in the aqueous solution in an amount of up to 900 mg/100 ml.

89. Dr. Amiji relies on his arguments concerning the claim 5 for claim 13. Ex. 1003 ¶¶283-284. I also rely on my opinions above for this claim.

Claim 17: A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising: administering, without prior dilution, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container to the patient at a rate of infusion and by a route of administration corresponding to the patient's age and degree of need of phosphorus replacement; wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus, no more than about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum

90. Dr. Amiji relies on his arguments concerning the above claims for most of claim 17. Ex. 1003 ¶¶287-288 and 293-296. I also rely on my opinions above for most of this claim.

91. As concerns the limitation related to a rate of infusion and by a route of administration corresponding to the patient's age and degree of need of phosphorus replacement, Dr. Amiji relies on the CMP-FDA label, specifically Section 2.3, Table 2 of the 2019 label. Ex. 1003 ¶¶290-292. As I explained above, however, this label is not prior art and even if it were, it is not a ready to use formulation.

Claim 18: The method of claim 17, wherein the rate of infusion is 6.8 mmol phosphates per hour or 15 mmol phosphates per hour.

92. Dr. Amiji opines that CMP-FDA discloses this limitation because it states that the maximum recommended infusion rate is “approximately phosphorus 15 mmol/hour.” Ex. 1003 at ¶298 (quoting Ex. 1008 at 3; Ex. 1027 at 5). I have explained above why the CMP-FDA label is not applicable prior art and in any event it does not disclose a rate of infusion of 6.8 mmol phosphates per hour.

Claim 19: The method of claim 17, wherein the route of administration is a central venous catheter.

93. Dr. Amiji relies again on CMP-FDA, which states that it is for intravenous infusion. Ex. 1003 at ¶300. Because the CMP-FDA is not prior art and the CMP Art is not ready to use (it must be diluted prior to administration), the CMP-FDA thus does not render claim 19 obvious.

Claim 20: The method of claim 17, wherein the solution is administered after storage of at least 3 months at 25° C. and 40% relative humidity.

94. Dr. Amiji states that “[a] POSITA would reasonably expect that, because CMP’s solution may be administered after 24-months of storage at 25°C and 60% RH, the CMP diluted solutions would also be suited for administration after 3-months of storage at 25°C and 40% RH.” Ex. 1003 at ¶304. I disagree. As I noted several times above, a POSA would not make any assumptions. Extensive tests would be needed to ensure that the formulation could be safely administered after the claimed storage conditions.

95. For all of the foregoing reasons, it is my opinion that the challenged claims are patentable over the prior art asserted in Ground 2.

C. The Challenged Claims are Not Unpatentable Over the Prior Art in Ground 3

96. As I already discussed above, a POSA would not combine the Ground 1 art with Nevakar, which is not related to the field of the invention. Dr. Amiji nevertheless relies on Nevakar for its packaging, arguing that it discloses the flexible polyolefin container recited in claim 9, the metallized overwrap in claim 10, the flexible polymeric container in claims 11-16, and the flexible container in claims 17-19 and the storage conditions of claim 20. Ex. 1003 at ¶¶313-352.

Claim 9: The solution of claim 1, wherein the solution is packaged in a flexible polyolefin container, optionally at a volume of between 100 mL and 1,000 mL, and optionally wherein the flexible polyolefin container is a flexible multilayer bag

97. Dr. Amiji posits that Nevakar's disclosure of a 100-1000 ml polymeric IV bag teaches this claim. Ex. 1003 at ¶¶315-316. I disagree. First, a POSA would not have selected Nevakar's IV bag without extensive tests. Additionally, Nevakar provides no reason why a POSA should specifically select a 100 ml volume bag. I therefore disagree with Dr. Amiji that Nevakar renders this claim obvious.

Claim 10: The solution of claim 9, wherein the flexible polyolefin container is further contained in a secondary metallized overwrap

98. Dr. Amiji opines that Nevakar discloses a metallized overwrap and that a POSA would have been motivated to use such an overwrap. Ex. 1003 at ¶319-321.

99. Notably, however, Nevakar mentions the possibility of using a metallized overwrap in passing, as just one of many examples or properties of bags. Nevakar does not specifically advocate to use such an overwrap and thus provides no motivation in my opinion. In any event, as noted above, experiments would be needed.

Claims 11-16: “flexible polymeric container”

100. Dr. Amiji only relies on Nevakar for the “flexible polymeric container” limitation in claims 11 through 16. Ex. 1003 at ¶¶323, 330, 332, 334, 336. For the reasons I explained above with respect to claims 9 and 10, I disagree with Dr. Amiji.

Claims 17, 18, and 19: “flexible container”

101. Dr. Amiji only relies on Nevakar for the “flexible container” limitation in claims 17-19. For the reasons I explained above with respect to claims 9 and 10, I disagree with Dr. Amiji.

Claim 20: The method of claim 17, wherein the solution is administered after storage of at least 3 months at 25° C. and 40% relative humidity

102. Dr. Amiji relies on Nevakar for this limitation, opining that the Nevakar containers purportedly “reduce permeability and, therefore, would reasonably be expected to prevent or substantially restrict evaporation.” Ex. 1003 at ¶¶351-352. Notably, Dr. Amiji does not cite to Nevakar for this proposition and it appears that he is simply offering his own opinion about what Nevakar discloses. For the reasons above, I disagree with Dr. Amiji on this point and I see nothing in

Nevakar that would cause a POSA to believe that the use of Nevakar's IV bags would meet this claim.

IX. CONCLUSION

103. In summary, it is my opinion that the claims of the '661 patent are not disclosed or suggested by the prior art.

104. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

105. 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: 9 August 2025

Signature: 