

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

PATENT OWNER'S PRELIMINARY RESPONSE

LIST OF EXHIBITS

Exhibit	Description
2001	U.S. Patent 10,632,150 (“Thomas”)
2002	Declaration of Gerald Sakowski
2003	C.A. 24-00846 (D. Del.), D.I. 61 Memorandum Opinion granting preliminary injunction motion dated 9/23/2024
2004	LexisNexis Patent Advisor Examiner Report for Al-Awadi, Danah J., retrieved April 14, 2025
2005	Comparison of Thomas (Ex. 2001) with WO2020/081118 (the “CMP-PCT”) (Ex. 1007)
2006	Declaration of Barrett Rabinow, Ph.D. dated July 16, 2025
2007	Curriculum Vitae of Barrett Rabinow, Ph.D.
2008	Rangel-Frausto et al., “Should we use closed or open infusion containers for prevention of bloodstream infections?” Annals of Clinical Microbiology and Antimicrobials 2010, 9:6 (“Rangel-Frausto 2010”))
2009	Rosenthal et al., “Prospective study of the impact of open and closed infusion systems on rates of central venous catheter–associated bacteremia,” American Journal of Infection Control, May 2004, Vol. 32, No. 3, pp. 135-141 (“Rosenthal 2004”)
2010	Franzetti et al., “Impact on rates and time to first central vascular-associated bloodstream infection when switching from open to closed intravenous infusion containers in a hospital setting,” Epidemiol. Infect. (2009), 137, 1041–1048 (“Franzetti 2009”)

Exhibit	Description
2011	Graves et al., Open versus closed IV infusion systems: a state based model to predict risk of catheter associated blood stream infections,” BMJ Open 2011; 2:e000188. doi:10.1136/bmjopen-2011-000188 (“Graves 2011”)
2012	Lutwick at al., “Managing and preventing vascular catheter infections: A position paper of the international society for infectious diseases,” International Journal of Infectious Diseases , 2019, 84:22-29 (“Lutwick 2019”)
2013	U.S. Patent 11,141,430 (“Koneru”)
2014	The Joint Commission. <i>Preventing Central Line–Associated Bloodstream Infections: Useful Tools, An International Perspective</i> . Nov 20, 2013. (“Joint Commission 2013”)
2015	Docket sheet as of June 27, 2025, in <i>Nivagen v. Amneal</i> , C.A. 24-00846 (D. Del.)
2016	Public version of Opening Brief in support of Preliminary Injunction, <i>Nivagen v. Amneal</i> , C.A. 24-00846 (D. Del.) D.I. 22
2017	Public version of Answering Brief on Preliminary Injunction in <i>Nivagen v. Amneal</i>
2018	Public version of Reply in support of Preliminary Injunction in <i>Nivagen v. Amneal</i>
2019	(Reserved)
2020	D.I. 93, Public version of Answer and Counterclaims (D.I. 91) in <i>Nivagen v. Amneal</i>
2021	D.I. 95 Brief in Support of Motion to Dismiss in <i>Nivagen v. Amneal</i>
2022	D.I. 101 Public Version of Opposition Brief on Motion to Dismiss in <i>Nivagen v. Amneal</i>

Exhibit	Description
2023	D.I. 102 Reply Brief on Motion to Dismiss in <i>Nivagen v. Amneal</i>
2024	Email from Yixin Tang to Defendants re: Sotera stipulation
2025	Comparison between FK-PI and CMP art
2026	Declaration of Mansoor M. Amiji, Ph.D. in <i>Nivagen v. Amneal</i> Preliminary Injunction briefing, D.I. 29
2027	European Centre for Ecotoxicology and Toxicology of Chemicals. <i>Guidance on Assessment Factors to Derive a DNEL, Technical Report No. 110</i> (“ECETOC 2010”)
2028	World Health Organization. <i>Dose-Responsive Assessment and Derivation of Health-Based Guidance Values</i> , in <i>EHC 240: Principles for Risk Assessment of Chemicals in Food</i> , 2nd. ed. (2020)
2029	van der Linden et al., “Ready-to-Use Injection Preparations versus Conventional Reconstituted Admixtures,” <i>Pharmacoeconomics</i> (2002), 20(8): 529-536 (“van der Linden 2002”)
2030	Declaration of Daniel Norwood, Ph.D.
2031	Curriculum Vitae of Daniel Norwood, Ph.D.
2032	Declaration of Barrett Rabinow, Ph.D. dated August 3, 2025

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I. INTRODUCTION¹

Petitioner misapprehends the disclosure and the claims it challenges, ignoring that the '661 patent paved the way for today's sterile, ready-to-use potassium phosphates solutions for injection. Instead, Petitioner exclusively relies on prior art that is neither sterile nor ready-to-use and does not teach or suggest the claimed formulations. Petitioner challenges the claims of the '661 patent based on three grounds, the first of which hinges on a legally flawed written description argument and the other two of which depend principally upon a determination that the so-called CMP Art in combination with Terlevich renders the challenged claims invalid. As explained below, however, (1) the CMP Art is admittedly not ready-to-use and not sterile when put to use and (2) Terlevich is plainly not sterile, requires manipulation prior to use, and in fact teaches away from the claims.

Furthermore, Petitioner cherry picks disparate elements from the selected prior art and unequivocally uses hindsight to piece those elements together in an attempt to arrive at the claims. Even after cherry picking, Petitioner provides no

¹ The patents being challenged before the Board and the parallel District Court are U.S. Patent No. 11,813,291 (the "'291 patent'") and U.S. Patent No. 11,925,661 (the "'661 patent'"). Petitioner challenges the patentability of the '661 in this IPR proceeding and that of the '291 patent in IPR No. 2025-00779.

motivation to combine the prior art and no basis for why a person of ordinary skill in the art would have a reasonable expectation that this disparate art could be successfully combined in the manner taught by the '661 Patent. As explained herein, a POSA would not leap to the assumptions Petitioner draws in its combinations but instead would need to conduct numerous experiments to arrive at the sterile, ready-to-use potassium phosphates solutions for injections recited in the challenged claims.

Moreover, the Petition repeats invalidity arguments already brought in a parallel ongoing District Court litigation—a point Petitioner fails to mention. Specifically, Petitioner tried and failed to establish a substantial question of invalidity as to the '661 patent in an unsuccessful bid to avoid a preliminary injunction and the District Court rejected Petitioner's invalidity theories, ruling in favor of Patent Owner. (Ex. 2003 (Preliminary Injunction Opinion)).

Petitioner's challenges are fatally flawed and Patent Owner, Nivagen Pharmaceuticals Inc. ("Patent Owner" or "Nivagen") respectfully requests that the Board deny the Petition for the reasons stated herein.

II. BACKGROUND

Hypophosphatemia is a clinical condition in which serum phosphate concentrations are less than 2.5 mg/dL (0.81 mmol/L). Ex. 1001 at 1:36-38. Hypophosphatemia can be life-threatening, and even mild cases can lead to serious complications affecting various organ systems, leading to muscle weakness,

respiratory failure, heart failure, and seizures and coma. *Id.* at 1:38-41. Hypophosphatemia is typically treated by administering phosphorus replacement, typically intravenously (“IV”); however, “serious cardiac reactions may occur as well as pulmonary embolisms due to pulmonary vascular precipitates.” *Id.* at 2:12-16. These serious cardiac and pulmonary risk factors render the accuracy of the concentration and infusion rate of the potassium phosphate critical for patient safety.

Furthering these risks, the prior art potassium phosphorus products—including those relied upon by Petitioner—are either supplied and stored as concentrates (and therefore require dilution, aseptic addition of excipients, and transfer to an appropriate container) or require other manipulation (such as opening a vent to allow outside air to get in contact with the injectable contents) prior to administration. Such dilution and other manipulation prior to use increases the risk of error and contamination and requires time and additional oversight, all of which may have serious consequences for patients in life-threatening conditions. *Id.* at 2:22-26. The prior art products also pose potential risks with respect to chemical stability and aluminum toxicity. *Id.* at 2:29-31.

In view of the drawbacks with prior art treatments, the inventors set out to create a sterile ready-to-use (RTU) solution. After significant testing, research and engineering, the inventors of the ’661 patent developed the sterile, RTU potassium phosphates solutions for intravenous administration disclosed in the specification.

Advantageously, the solutions disclosed and claimed in the '661 patent “exhibit excellent storage stability over extended periods of time, include a suitable tonicity agent, have a desirable phosphate to potassium ratio, and have an aluminum content that is equal or less than 50 mcg/L.” *Id.* at 3:13-16. Such solutions do not require any dilution or other manipulation prior to use and “can be administered as a single unit at a rate of administration that will not require specific calculations.” *Id.* at 3:19-21. The advantages of the claimed RTU solutions over the prior art 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.” Ex. 2030 at ¶ 22.

Developing ready-to-use drugs, however, involves unique obstacles and challenges and requires meticulous focus on addressing the combined challenges of stability, sterility, manufacturing, regulatory compliance, and formulation specifics to ensure safe and effective patient care. These formulations need to stay stable during storage, which means preventing degradation from factors like temperature, humidity, and oxidation. Ex. 2030 at ¶ 23. It is essential to achieve the right solubility, bioavailability, and viscosity, which is particularly important for injectable products and patient outcomes. *Id.* The choice of excipients and packaging materials must safeguard both the effectiveness and shelf life of the medication and prevent leaching or interaction that could compromise the drug’s stability or

efficacy. *Id.* Stringent sterilization procedures are necessary during production to ensure sterility, backed by comprehensive validation. *Id.*

As Dr. Norwood (Patent Owner's expert on the issue of obviousness) explains:

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.

Ex. 2030 at ¶ 24. The specification of the '661 patent sets forth numerous examples of the tests performed by the inventors in arriving at the claims.

Notably, Petitioner and its expert, Dr. Amiji, ignore the challenges and requisite testing in preparing RTU solutions. Instead, they use the claims of the '661 patent as a roadmap and simply assume that a POSA would take the concentrated

formulation disclosed in the CMP Art, dilute it, add sodium chloride as a tonicity agent, and put it in the container disclosed in Terlevich. There are several significant problems with Petitioner's theory summarized here and explained in detail below. First, a POSA would never make any assumptions about critical parameters such as chemical and physical stability, compatibility of the formulation with the packaging system, impurities, shelf-life, sterilization, aseptic processing, and quality control, 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. Ex. 2030 at ¶¶ 24, 58. Second, even if a POSA were to draw certain assumptions and put a diluted version of the CMP formulation in the Terlevich container, they still would not arrive at the claimed sterile, RTU product because (1) a diluted solution in the Terlevich container is neither RTU nor sterile when it is used, (2) such a diluted solution would not contain the claimed tonicity agent, and (3) the process of dilution and transfer would have contaminated the formulation. Ex. 2030 at ¶¶ 34, 44-46, 52-54.

III. REFERENCES RELIED UPON BY PETITIONER

A. Nivagen-1

Nivagen-1 is U.S. Patent App. Pub. No. 2022/0110969, filed as the '001 application—the priority application to the '661 patent—and published April 14, 2022. Ex. 1006, Cover. Petitioner relies on Nivagen-1 only with respect to Ground

1, contending that the challenged claims are unsupported by the disclosures in Nivagen-1 such that the priority application is anticipatory prior art.

B. The CMP Art

The CMP Art consists of two related references originating from CMP Development LLC (“CMP”). The predominant reference is International Patent Application Publication No. WO2020/081118 (the “CMP-PCT”) (Ex. 1007) purporting to disclose a sterile composition for injection comprised of potassium phosphates. The secondary reference is a “Highlights of Prescribing Information” document related to the same composition (the “CMP-FDA”) (Ex. 1008). As admitted by Petitioner and its expert, Dr. Amiji, the CMP Art is not a ready-to-use formulation. Petition at 35 (“CMP-PCT does not disclose that its solutions are ready-to-use.”). Additionally, 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). Furthermore, a POSA would recognize that diluting the product can compromise sterility due to handling during transfer and mixing. Ex. 2030 at ¶ 45. These diluted solutions are often only suitable for short-term use and may develop particulates or discoloration, further indicating a lack of sterility. *Id.*

As concerns the CMP-FDA label, Petitioner states that it “likely” published in September 2019 and certainly by September 23, 2020. Petition at 22. But the label that Petitioner claims was “likely” published in September 2019 (Ex. 1008) states on its face that it does not contain “full prescribing information” from the FDA-approved drug label and Petitioner provides no evidence of its actual publication. The sole evidence Petitioner cites to for the September 23, 2020 date are two declarations (Ex. 1003 (declaration of Dr. Amiji) explaining how he used the Wayback Machine and Ex. 1023 (declaration of Mina Ching from the Internet Archive explaining how the Wayback Machine works)) and some screenshots from the Wayback Machine web site. However, this does not show that the “Highlights” document was sufficiently publicly accessible such that a POSA, exercising reasonable diligence, could have located it on the internet. Indeed, Petitioner offers only one statement of its expert that “generally” FDA drug labels are published within two business days of the drug label approval date. Ex. 1003 at ¶ 94. But the sole evidence Dr. Amiji cites to for this proposition is a current FDA announcement merely stating that at the present time, FDA “typically add[s] information to Drugs@FDA about approved drug and biological products within two business days of approval.” *Id.* at ¶ 93. What FDA “typically” does at this time is not reflective of its practice back in 2020. Moreover, the FDA statement does not indicate, either

back in 2019, 2020 or today, whether any “highlights” information similar to Ex. 1008 may be posted within two business days of approval, or ever.

C. Terlevich

The “Terlevich” reference (Ex. 1009) discloses a Phosphate Polyfusor® (“PPF”) product, which was briefly available in the United Kingdom (it was never approved in the United States). Petitioner claims that Terlevich is an RTU product simply because it is pre-diluted and in a semi-rigid container. Petition at 36. But in fact, the PPF was not a sterile, RTU product and had many drawbacks and potential dangers to the patients that were well-known and well-published in the relevant field of art. Ex. 2006 at ¶2.

Specifically, Terlevich discloses that “[a] Polyfusor is a sealed *semi-rigid cylindrical polyethylene container*, with a twist-off seal at one end and a ring tab at the other.” Ex. 1009 at 6 (emphasis added). 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. Ex. 2006 at ¶ 21. Such a semi-rigid plastic container is a noncollapsible container, which “must be vented externally to allow air to enter and the fluid to egress. *Id.*; *see also* references cited and quoted therein. Air ingress could then lead to microbial contamination of the remaining fluid within the container, particularly in hospital environments. *Id.* at ¶ 22; *see also* references cited and quoted therein. These open systems such as the

Terlevich system caused increased morbidity and mortality, significantly higher costs to treat the bloodstream infection, and an overburdened healthcare system, which could potentially deprive other patients of a critical care bed, depending upon resource availability. *Id.* at ¶¶ 34-45.

Terlevich teaches away from the claimed invention given the significant problems with such a device. When a piece of prior art “suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant” the piece of prior art is said to “teach away” from the claimed invention. *In re Gurley*, 27 F.3d 551, 553 (Fed.Cir.1994). A POSA would neither turn to nor would a POSA be motivated to combine Terlevich with the CMP Art with any reasonable expectation of success. Ex. 2030 at ¶ 36.

D. Ogawa

Petitioner optionally relies on Ogawa as disclosing low aluminum. 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 8. A POSA would not have found Ogawa to be relevant 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. Ex. 2030 at ¶¶ 37-39.

E. Nevakar

Finally, Petitioner also cites Nevakar (Ex. 1011) in Ground 3 as additional art that purportedly discloses “flexible polymeric containers suited for use with ready-to-use solutions, which containers may include a secondary metallized overwrap.” Petition at 66-68. Nevakar is not specific to any potassium phosphate compositions but instead relates to sterilizable epinephrine compositions. 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. Ex. 2030 at ¶¶ 41-42.

IV. PETITIONER PROVIDES NO RATIONALE OR MOTIVATION TO COMBINE THE REFERENCES WITH A REASONABLE EXPECTATION OF SUCCESS AND USES IMPROPER HINDSIGHT

“It is not sufficient to demonstrate that each of the components in a challenged claim is known in the prior art,” because there must also be a motivation to combine and a reasonable expectation of success. *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *Microboards Tech., LLC d/b/a Afinia v. Stratasys, Inc.*, IPR2015-00287, Paper 13 at 14 (PTAB May 28, 2015). Evidence showing there was no reasonable expectation of success supports a conclusion of nonobviousness.

In re Rinehart, 531 F.2d 1048 (CCPA 1976); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). For the reasons below, due to the failures in the prior art, the many variables and parameters at issue, and the challenges in formulating RTU injectables, a POSA at the time of the invention would not have been motivated to combine Petitioner's references with a reasonable expectation of success.

A. There Is No Motivation to Combine the Prior Art

Turning first to whether there is a motivation to combine Petitioner's chosen art, a POSA 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 optionally 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. Ex. 2030 at ¶ 43.

Petitioner's compilation of prior art and unsupported assumptions the combination would work evidences hindsight. As Dr. Norwood explains, Dr. Amiji "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.” Ex. 2030 at ¶ 44.

For example, the CMP-PCT—Dr. Amiji’s primary reference—is a document focusing on how the amounts of monobasic potassium phosphate (KMP) and dibasic potassium phosphate (KDP), as well as aluminum levels, may need adjustment due to the chemicals being stored in glass vials. Ex. 1007 at 2:14-28. However, these considerations do not directly relate to the challenged claims and a POSA therefore would view CMP Art as irrelevant. Additionally, the CMP-PCT outlines several challenges associated with formulating pharmaceutical preparations and requirements for testing their stability. It describes how twelve different formulations were created, each with varying concentrations of KMP and KDP and differences in pH and storage conditions. Ex. 2030 at ¶¶ 46-48. The purpose of these tests was to evaluate how storage factors, such as vial composition and environmental conditions, might influence the stability and efficacy of the formulations. The only set of storage conditions that proved satisfactory was storage at 4-8 degrees Celsius for 18 months. Ex. 1007 at 19:1-5.

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. Ex. 2030 at ¶ 49. Indeed, as explained above, the only reference that Petitioner

contends discloses a ready-to-use product—the Terlevich reference—not only teaches away from the claimed invention, it also underscores the challenges in developing a sterile, ready-to-use potassium phosphates in sodium chloride solution. This is because the PPF system disclosed in Terlevich is (1) not RTU (the user first needs to open the valve and put the system in contact with air, which serves as driving force); (2) not sterile (the user has to expose the formulation to air, which carries with it significant contaminants, especially in a hospital, and can be deadly to the already vulnerable patients being treated); and (3) is but one of many containers available to a POSA. Ex. 2030 at ¶¶ 51-54. A POSA thus would not be motivated to combine the CMP-Art with Terlevich to arrive at the claims. *Id.*

A POSA also would not have combined the CMP-Art with Terlevich to arrive at the claimed phosphorus concentration. The concentration of phosphorus in the formulation is but one of numerous factors that the formulator would have to account for, such as stability, sterility, particle formation, tonicity, and pH, and patient age, weight, severity. Ex. 2030 at ¶ 75. There are many reasons why a concentrate solution may be preferred such that a POSA would not be motivated to develop an RTU formulation, much less one having the claimed phosphorus concentration.

Additionally, 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. Ex. 2030 at ¶¶ 38, 61.

Furthermore, in Ground 3, Petitioner relies on Nevakar as disclosing a secondary metallized overwrap. But Nevakar relates to epinephrine compositions in containers having a volume of between 100 mL and 1,000 mL. Petitioner provides no sound reasons why a POSA would turn to Nevakar or combine it with the other Ground 2 prior art. In any event, a POSA would not have simply selected a container because it was used for an RTU-product when that product, its formulation, pH requirements, sterility requirements, stability requirements, and storage conditions all are different from the novel formulation being invented. Ex. 2030 at ¶¶ 62-63. 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 as evidenced by the specification of the challenged patent. *Id.*

B. There Is No Expectation of Success

As concerns the reasonable expectation of success aspect of the inquiry, Petitioner argues that the asserted combinations demonstrate the existence of all the elements of the claims, but Petitioner does not explain why or how a POSA could combine the prior art with a reasonable expectation of success. Petitioner simply states, without explanation, that “it would be straightforward to apply the teachings of Terlevich to CMP-PCT to achieve RTU solutions.” Petition at 37. Petitioner

makes the same *ipse dixit* statement with respect to combining the other references. *See* Petition at 44 (Ogawa), 66 (Nevakar). Failure to provide such reasoning justifies denial of the petition. *See, e.g., Apple Inc. v. Contentguard Holdings, Inc.*, IPR2015-00453, Paper 9 at 12-16 (PTAB July 13, 2015).

But in fact, there could be no reasonable expectation of success in combining these references to come up with the invention disclosed in the challenged patent at least because a POSA would know that “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.” Ex. 2030 at ¶ 66. The law is well-settled that, if the proposed combination of the prior art would be unsatisfactory for its intended purpose, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *See, e.g., In re Ratti*, 270 F.2d 810, 813 (C.C.P.A. 1959); *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Here, if one were to combine the prior art advanced by Petitioner, the combination still would not be sterile and ready to use.

Furthermore, “to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988). Similarly, prior art fails to provide the requisite

“reasonable expectation” of success where it teaches merely to pursue a “general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” *Id.*

This is a case where there are numerous parameters to vary, and the prior art only gives general guidance. Specifically, as Dr. Norwood testifies at length, even if a POSA were to consider putting the CMP Art formulation in an RTU bag, extensive experimentation would be required. *See, e.g.,* Ex. 2030 at ¶¶ 66-71. Transmuting the CMP concentrated potassium phosphates solution into pre-mixed bags may introduce risks for chemical stability issues and physical stability issues, which may be heightened during the storage period at room temperature afterwards. *Id.* at ¶ 69. From a chemical perspective, dilution can present 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. *Id.* This underscores the many variables and parameters at issue, all of which would require extensive tests. Additionally, alterations in the packaging material, especially for solutions, may significantly increase the risk, which combined with sterilization issues, raises potential problems for a formulator. *Id.* Because of the many unknowns, a POSA would not have had

a reasonable expectation of success in applying Petitioner's prior art to a sterile, RTU formulation.

For all of the foregoing reasons, the lack of any reasonable expectation of success warrants a finding of nonobviousness. *Regents of University of California v. Broad Institute, Inc.*, 903 F.3d 1286, 1291-94 (Fed. Cir. 2018) (affirming Board's finding of nonobviousness where experts testified there were many variables and unknowns that provide a lack of any expectation of success); *Endo Pharms. Inc. v. Actavis LLC*, 922 F.3d 1365, 1374 (Fed. Cir. 2019) (affirming district court's finding of no expectation of success where expert testified many variables would need to be tested).

C. Petitioner Uses Hindsight Reconstruction

As explained on several occasions above, Petitioner uses hindsight to arrive at the claims. It is well established that “[c]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references.” *Grain Processing Corp. v. Am.-Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (internal quotation marks omitted). Thus, “rejections on obviousness grounds cannot be sustained by mere conclusory statements.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

The Petition is replete with hindsight reconstruction. Perhaps the clearest example of this is where the Petition states that a POSA looking at the CMP Art

would automatically know to dilute the CMP Art by a factor of 30. Petition at 37-

39. The Petition 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.

Id. at 38. Tellingly, in the Petition concerning the challenged claims of the related '291 patent, Petitioner makes the exact same assumption as to what factor a POSA would dilute to, but there Petitioner arbitrarily picks a factor of 20 because that is what would be required to arrive at the challenged '291 patent. Petitioner here picks dilution by a factor of 30 to arrive at the challenged '661 patent claims. It is clear that Petitioner is simply using hindsight to pick arbitrary disclosures and arrive at the claims. In any event, a POSA would not draw any such assumptions concerning critical parameters that relate to patient safety and instead would have to conduct extensive tests and set parameters. Ex. 2030 at ¶¶ 57-60.

Petitioner's reliance on Ogawa concerning low aluminum content similarly reflects hindsight bias. Petition at 42-44. 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.

This is not a case of substituting or combining prior art elements according to known methods to yield predictable results, or a case of applying a known technique to improve similar devices in the same way to yield predictable results. The extensive tests that were performed as summarized in the specification belie that notion. Ex. 2030 at ¶ 67. Petitioner instead “us[es] the patent in suit as a guide through the maze of prior art references” to reach the claims in suit. *Grain Processing*, 840 F.2d at 907. This is the quintessential example of “allow[ing] hindsight reconstruction of references to reach the claimed invention,” against the guidance of the Federal Circuit. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1374 n.3 (Fed. Cir. 2012).

V. PETITIONER’S GROUND 1 ANTICIPATION ARGUMENT IS FLAWED

Petitioner argues that the ’001 application (“Nivagen-1” or Ex. 1006) does not provide written description support for the phosphorous concentrations recited in the challenged claims and, as such, is anticipatory prior art. Petition at 5-8. Petitioner recognizes that Nivagen-1 broadly discloses daily and maximum phosphorous concentrations in a sterile RTU solution but nevertheless asserts that these disclosures do not provide written description support for the lower limit of the claimed phosphorous range. *Id.* at 9-10.

It is well settled that the specification need not expressly recite the claimed range to provide written description support. *See Rai Strategic Holdings, Inc. v.*

Philip Morris Products S.A., 92 F.4th 1085, 1090 (Fed. Cir. 2024) (explaining that a broader description can—and often does—provide ample support for a narrower claimed range and citing cases).

Here, the claims recite a range of “between [about] 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous.”

At least paragraphs 44 and 45 of Nivagen-1 (Ex. 1006) provide written description support, stating:

[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).

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. Ex. 2032 at ¶ 20. A POSA would further understand from this disclosure, and the disclosure of not more than 18 mmol/100 ml phosphorus, 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. *Id.*

Table 1 also discloses the ranges of (a) not more than 2.7 or 5.5 mmol/100 ml for use in pediatric patients less than 12 years of age, and (b) not more than 6.8 or 18 mmol/100 mL for adults and older children:

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)

Notably, the introductory text for Table 1 states that the treatment that **must be adjusted to the patient's age and particular need**. A POSA would understand from this disclosure that a “maximum recommended daily concentration and infusion rate as shown in Table 1,” must mean a *downward* adjustment from that maximum. Ex. 2032 at ¶ 23. That is, a POSA 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.” *Id.* The lower end of the claimed range is thus adequately described.

Regarding the upper limit of the claimed range, paragraph [0005] of Nivagen-1 states that phosphorus therapy is administered at a rate not exceeding the maximum recommended concentration and infusion rate. A POSA would interpret this as ensuring the rate remains below the maximum, with adjustments made for the patient’s age and needs—meaning adjustments can only decrease the rate. Ex. 2032 at ¶ 24. Thus, the disclosed maximum concentration of 18 mmol/100 mL for adults and older children adequately discloses the claimed maximum concentration of 15 mmol/100 mL. *Id.* at ¶¶ 24-25.

Petitioner also argues that, “even if the above ‘not more than’ disclosures constitute a disclosure of phosphate concentrations for the sterile, RTU solutions (they do not), such disclosures still fail to disclose the claimed Phosphorous Range.” Petition at 10. Petitioner overlooks that a POSA would consider toxicity in determining how much downward adjustment would be appropriate for an injectable product. Ex. 2032 at ¶¶ 27-28. It was well known at the time of the invention that the most sensitive individuals are typically children, particularly neonates and that the default is to adjust by a factor of 10. *Id.* at ¶¶ 27-30. Accordingly, a POSA would divide an adult rate of 15 mmol/100ml by 10 to obtain 1.5 mmol/100ml, which is not more than 2.7 mmol/100ml. *Id.*

Petitioner also notes that Table 8, Item 9 provides for a maximum 5% deviation from the target concentration of 4.65 mg/mL (15 mmol/100 ml) allowed upon release, arguing that the lowest concentration allowed by the '661 patent itself would be 2.565 mmol/100 ml (a change of 5% as compared to 2.7 mmol/100 ml). Petition at 10-11. The “maximum 5% deviation from the target” requirement concerns the designated concentration of a product for manufacturing purposes (i.e. for reliability in manufacturing and quality control); it is not any limitation on the product’s intended or labeled concentration range. This is a quality parameter typically required to designate the permissible excursion of actual commercial product from the labeled concentration, as required by FDA and the USP, not a medical parameter. Ex. 2032 at ¶ 33.

Moreover, the claimed range of 1.5 mmol/100 mL to 15 mmol/100 mL could readily be envisioned by a POSA having the relevant medical knowledge. Ex. 2032 at ¶¶ 34-38. As mentioned above, a POSA would take into account toxicity issues and would know to make adjustments for the patient’s age and needs.

**VI. THE COMBINATION ASSERTED IN GROUND 2 FAILS TO
RENDER THE CHALLENGED CLAIMS OBVIOUS**

A. Petitioner Does Not Show That All Elements Exist In The Art

1. 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 6.5 and 7.5

Petitioner contends that the CMP Art in combination with 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” 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.” Petitioner is wrong for several reasons.

First, none of the Ground 2 references teach or disclose a solution that is both sterile and ready-to-use. As the District Court previously held in a related proceeding granting Nivagen a temporary restraining order: “the Court is persuaded that the sterility and ready-to-use properties of the patented invention alone make it more likely than not that the [challenged] patent is not obvious.” *See* Ex. 2003 at 10. The CMP Art needs to be diluted, a process that can easily compromise sterility, as even Petitioner’s expert admits (*e.g.*, Ex. 1003 at ¶ 199). Terlevich exposes the

formulation to outside air, which introduces contaminants and significantly affects sterility. Ex. 2030 at ¶ 53; Ex. 2006 at ¶¶ 21-27. Ogawa is inapposite.

Second, 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 Petitioner relies on the CMP-FDA label (which is not prior art) as disclosing this limitation (*e.g.*, Petition at 40-41), it is important to note that the CMP formulation described in CMP-FDA and CMP-PCT did not in fact contain sodium chloride. The CMP-FDA label instructed pharmacists to add that excipient. *Id.* But just because the CMP formulation—which had notable differences from the claimed formulation—added sodium chloride after dilution, this does not make the claim limitation obvious as it would require extensive testing and evaluation to determine which tonicity agent to use with the claimed formulation. Ex. 2030 at ¶ 74.

Third, the prior art combination does not disclose “wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous.” Petitioner 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. Petition at 38. A POSA would not draw such assumptions and instead would consider the many differences between the CMP-PCT and Terlevich and would run numerous tests to determine the ideal phosphorous concentration. Ex. 2030 at ¶ 75. As discussed above, Petitioner’s

argument relies on hindsight by linking unrelated references to claim that a POSA would—without testing—dilute CMP-PCT solutions by a factor of 30 to arrive at a RTU product. Developing RTU formulations presents numerous challenges, and a POSA would test viability rather than make such assumptions. *Id.*

Fourth, Petitioner’s “optional” reliance on Ogawa in addition to the CMP Art as teaching low aluminum is misplaced. The formulations disclosed in the CMP Art and Ogawa were in glass vials. It was known that glass vials were problematic in that they will increase aluminum content. But a POSA would never use glass vials for an RTU product and thus would not have considered the disclosures in these references in the first instance. Ex. 2030 at ¶ 76.

Fifth, a POSA would not have thought that the CMP-PCT teaches the pH limitation of claim 1 because it teaches its solutions have pH of about 6.5 to about 7.5. There are several notable differences between the formulation described in the CMP-PCT and that of the claims, which could influence pH. For instance, the CMP-PCT is neither diluted nor ready-to-use (RTU). Furthermore, the CMP-PCT employed dextrose rather than sodium chloride. Without comprehensive testing, a POSA could not reliably determine whether such modifications would impact the pH.

2. 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

Petitioner argues that CMP-PCT in view of Terlevich teaches this limitation because “[t]he molar ratio of KDP:KMP in this solution is 1.34.” Petition at 50. A molar ratio of 1.34 does not make 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. Ex. 2030 at ¶ 78. A POSA would not expect a molar ratio in a concentrated solution to necessarily stay the same after the solution is diluted. *Id.*

3. 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

Petitioner relies on the CMP Art and Terlevich for this limitation, and adds no new arguments. Petition at 51. For the reasons above, Petitioner’s contention that this claim is obvious should be rejected. Additionally, neither Terlevich nor the CMP-PCT constitute ready-to-use formulations as in the challenged patent. The development of an appropriate RTU formulation involves numerous variables, discussed above. Furthermore, even if one were to theoretically combine the art to suggest that the potassium content in an RTU solution should be as claimed, a POSA

would refrain from making assumptions and instead conduct thorough testing to evaluate factors such as stability, pH, and other relevant considerations. Ex. 2030 at ¶ 79.

4. 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

Petitioner relies on the CMP Art in view of Terlevich as making this claim obvious. Petition at 51. The CMP-PCT contains 470 mEq per 100 mL potassium. Ex. 1007 at 17:1-8. Petitioner posits that it was somehow obvious to dilute the CMP-PCT solution by a factor of 30.

CMP-PCT did not constitute a ready-to-use formulation as claimed in the challenged patent. Numerous variables influence the development of an appropriate RTU formulation, as previously detailed. Even assuming, *arguendo*, that CMP-PCT could be combined with Terlevich to suggest to a POSA that the potassium concentration in an RTU solution should not exceed 22 mEq/100 mL—which is not the case—a POSA would not rely on presumptions. Rather, they would need to conduct extensive testing to confirm key attributes such as stability, pH, and other critical factors. Ex. 2030 at ¶ 81.

5. 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

Petitioner relies on the CMP Art and Terlevich for this claim limitation. Petition at 51-52. There are important distinctions between the CMP-PCT and Terlevich formulations and the claims, including whether the solution is diluted or ready-to-use (RTU), and whether dextrose is used in place of sodium chloride. Thus, 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. Ex. 2030 at ¶ 82.

6. 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

Petitioner relies on CMP-PCT in view of Terlevich as disclosing this claim limitation. Petition at 52-53. Importantly, however, neither CMP-PCT nor Terlevich disclose any particle count of a diluted solution placed in a flexible container after the steps recited in claim 6. Instead, 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 Petition nevertheless asserts 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.” Petition at 53. This analysis is flawed because it is based on an assumption that Terlevich’s semi-rigid containers wouldn’t affect stability, including particle counts. 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. Ex. 2030 at ¶ 87. The CMP-PCT therefore does not render this claim obvious.

7. 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

Petitioner again makes assumptions similar to those for claim 6. As previously discussed, there exist numerous distinctions between the prior art formulations and packaging and those specified in the claims, which may influence both particle formation and the variations in phosphorus and potassium concentrations over time. A POSA would not presume that the stability data disclosed in CMP-PCT is directly applicable to an RTU formulation. Ex. 2030 at ¶ 85.

8. 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

Petitioner advances only limited arguments with respect to this claim and instead relies on its arguments concerning the foregoing claims. For the reasons set forth above, Petitioner's arguments concerning the foregoing claims should be rejected. Additionally, Petitioner fails to account for the differences between claim 11 and the foregoing claims, including "premixed" and "about 15 mmol/100 ml phosphorus." Petitioner has not carried its burden with regard to this claim.

As concerns Petitioner's contention 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,'" this is mere wordsmithing. A POSA 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. Ex. 2030 at ¶ 86.

9. 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.

Petitioner advances no new arguments concerning this claim and instead relies on its analysis of the above claims. Petition at 57. For the reasons stated above, Petitioner's arguments should be rejected.

10. 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.

Petitioner advances no new arguments concerning this claim and instead relies on its analysis of the above claims. Petition at 57. For the reasons stated above, Petitioner's arguments should be rejected.

11. 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

Petitioner again relies on its arguments concerning the above claims for most of claim 17 and again fails to take into account the differences between claim 17 and

the above claims. Petition at 58. For the reasons set forth above, Petitioner's arguments concerning the foregoing claims should be rejected.

The only elements the Petition addresses separately are the intravenous administration limitation and the limitation concerning a rate of infusion and by a route of administration corresponding to the patient's age and degree of need of phosphorus replacement, relying predominantly on the CMP Art and Terlevich. Petition at 58-59. For the reasons stated above, a POSA would not have combined the CMP Art with Terlevich with any reasonable expectation of success and Petitioner's arguments fail as a result. Additionally, the CMP-FDA label relied on by Petitioner only states to "[i]ndividualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake." Ex. 1008 at 4; Ex. 1027 at 6. This makes no mention of the patient's age and again, it relates to a concentrated formulation that the pharmacist would need to individualize based on the health care provider's specific instructions. It is not RTU and does not render this claim obvious. Ex. 2030 at ¶ 91.

12. 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.

Petitioner asserts that CMP-FDA discloses this limitation because it states that the maximum recommended infusion rate is "approximately phosphorus 15

mmol/hour.” Petition at 60. The CMP-FDA label is not prior art, and, in any event, it does not disclose a rate of infusion as claimed. It provides no disclosure of 6.8 mmol phosphates per hour and only “recommends” administration at 15 mmol/hour. Ex. 1008 at 3; Ex. 1027 at 5. A POSA would not have found this claim obvious over the prior art. Ex. 2030 at ¶ 92.

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

Petitioner relies again on CMP-FDA, which states that it is for intravenous infusion. Petition at 60. 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. Ex. 2030 at ¶ 93.

14. 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

Petitioner relies on its arguments concerning claims 6-8 and further states that “[a] POSITA would reasonably expect that, when employing an appropriate, conventional RTU container, such as the semi-rigid containers described by Terlevich, the diluted CMP’s solutions would be suited for administration after 3-months of storage at 25°C and 40% RH.” Petition at 61. As explained in detail above, however, 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. Ex. 2030 at ¶ 94.

B. Petitioner's Prior Art Combination Does Not Render the Claims Obvious

For all of the foregoing reasons, the Ground 2 combination asserted by Petitioner does not and cannot render the challenged claims of the '661 patent obvious. To summarize, multiple limitations that are critical to all the challenged claims are missing from the asserted combination. Petitioner's references are all directed solely to solutions with limitations (*e.g.*, not RTU and not sterile) that every challenged claim overcomes. As explained above, these shortcomings are the opposite of and teach away from the potassium phosphates solution claimed in the '661 patent. That is, the prior art nowhere discloses a sterile, ready-to-use formulation, whereas these elements are the *sine qua non* of the '661 patent. This is fatal to the Petition. *Kinetic Concepts, Inc.*, 688 F.3d at 1361, 1366 (obviousness not established where limitations critical to all claims were not disclosed in any asserted reference and a POSA had no reason to combine the prior art references to arrive at the claimed invention); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305-06 (Fed. Cir. 2015) (finding claims not obvious and holding that the prior art teachings that BAK should be minimized teaches away from the patent's use of higher concentrations of BAK).

Moreover, the inventions of the '661 patent would not operate as intended if constructed from the asserted combination because the combination would still use a semi-rigid, non-RTU and non-sterile container, and hence the prior art combination

is fatally inadequate. As a result, Petitioner fails to establish that it is likely to prevail on its obviousness assertion.

VII. THE COMBINATION ASSERTED IN GROUND 3 FAILS TO RENDER THE CHALLENGED CLAIMS OBVIOUS

A. Petitioner Does Not Show That All Elements Exist In The Art

Petitioner's Ground 3 arguments underscore that its Ground 2 references fail to render obvious the challenged claims. The novelty of the claimed invention lies not only in the precise diluted formulation as claimed (a formulation that could only be arrived at after extensive testing) but also the precise RTU packaging used (also subjected to extensive testing). *See, e.g.*, Ex. 1001 (disclosing numerous tests, Figures and Tables to arrive at the claims). Because none of the Ground 2 references teach or disclose that putting a diluted version of the CMP Art in a Terlevich container would meet the claims, Petitioner additionally relies on Nevakar. Specifically, the sole difference between Petitioner's arguments in Ground 2 versus those in Ground 3 relate to the claimed container, *i.e.*, a flexible polyolefin or polymeric container, a volume of 100 ml, or a secondary metallized overwrap. Petition at 61-68.

Nevakar, however, is inapposite art. 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]. Additionally, Nevakar merely "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]. It would not have been obvious to a POSA reading Nevakar to specifically use the containers (much less a 100 ml container) claimed in the ’661 patent. Ex. 2030 at ¶¶ 40-42.

1. 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

Petitioner asserts that Nevakar’s disclosure of a 100-1000 ml polymeric IV bag teaches this claim. Nevakar provides no reason why a POSA should specifically select a 100 ml volume. Moreover, Nevakar discloses a wide range of bags to use with its epinephrine solutions. As explained above, a POSA would not assume that any of the many bags disclosed in Nevakar (for epinephrine) would work with a flexible polyolefin container for an RTU potassium phosphate solution recited in the claims. Ex. 2030 at ¶ 97.

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

Petitioner recognizes that Nevakar merely discloses that its epinephrine bags “may” be contained in a metallized overwrap. Petition at 65. 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 to a POSA. Ex. 2030 at ¶ 99.

3. Claims 11-16: “flexible polymeric container” and Claims 17-19: “flexible container”

Petitioner primarily relies on its Ground 2 arguments for claims 11-19 (and indeed, entirely on its Ground 2 arguments with respect to claims 12-13 but additionally relies on Nevakar for these limitations; however, for the reasons stated above, Nevakar does not teach or disclose these limitations and a POSA would need to conduct undue experimentation to come up with a formulation that worked in such containers. Ex. 2030 at ¶¶ 100-01.

4. 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

Petitioner fails to explain how Nevakar adds to its Ground 2 art with respect to this limitation. There are no citations to Nevakar for claim 20 and in any event, there is nothing in Nevakar that would cause a POSA to believe that the use of Nevakar’s IV bags would meet this claim. Ex. 2030 at ¶ 102.

B. Petitioner’s Prior Art Combination Does Not Render the Claims Obvious

For all of the foregoing reasons, the Ground 3 combination asserted by Petitioner does not and cannot render the challenged claims of the ’661 patent obvious. Nevakar adds nothing to the Ground 2 art and a POSA would not have simply selected the Nevakar epinephrine container when its formulation, pH requirements, sterility requirements, stability requirements, and storage conditions

all are different from a potassium phosphates formulation. Ex. 2030 at ¶ 63. Instead, a POSA would have to conduct extensive experiments and carefully control these parameters. *Id.*

VIII. PETITIONER IGNORES SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

Petitioner does not address secondary considerations of non-obviousness, including the long-felt need, commercial success, and Petitioner's copying of the invention. Indeed, the challenged patent has already been shown to be novel and successful in a related District Court proceeding, where the Court awarded a preliminary injunction against Petitioner's likely infringing commercial product and set the bond at approximately \$30 Million. Ex. 2015 at D.I. 63 (entered 9/24/2024). Furthermore, the specification recognizes the novelty of a sterile RTU injectable treatment over prior potassium phosphorous products. *See* Ex. 1001 at 2:16-21. Because Petitioner has not demonstrated a reasonable likelihood of success on any grounds, and to avoid unnecessary burden on the Board, Patent Owner does not submit specific evidence relevant to secondary considerations at this stage.

IX. CONCLUSION

For the foregoing reasons, institution should be denied.

Respectfully submitted,

Dated: August 19, 2025

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CERTIFICATION OF WORD COUNT 37 C.F.R. § 42.6(e)

Pursuant to 37 C.F.R. §42.24(d), Patent Owner hereby certifies that the word count for the foregoing PATENT OWNER'S PRELIMINARY RESPONSE is 9394 words, which is within the limit set in 37 C.F.R. §42.24(b)(1). This word count does not include the table of contents, table of authorities, exhibit list, certificate of word count, and certificate of service. This word count was prepared using Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned certifies that on August 19, 2025, a complete and entire copy of this PATENT OWNER'S PRELIMINARY RESPONSE was provided by email to the Petitioner by serving the correspondence address of record as follows:

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