UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, INC.,
Petitioner
v.

NIVAGEN PHARMACEUTICALS, INC.
Patent Owner.

IPR2025-00779
Patent No. 11,813,291

PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1, 3-11, 14-15, AND 17-20 OF U.S. PATENT 11,813,291

TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,813,291 (the "'291 patent")
1002	File history for the '291 patent
1003	Declaration of Dr. Mansoor Amiji
1004	File history for U.S. Patent Application No. 18/460,941
1005	File history for U.S. Provisional Patent Application No. 63/090,518 ("'518-PRV")
1006	RESERVED
1007	International Patent Application Publication No. WO2020/081118 ("CMP-PCT")
1008	Federal Drug Admininstration Drug Label for "POTASSIUM PHOSPHATES injection, for intravenous use," September 2019
1009	Terlevich, A., et al. "Refeeding syndrome: effective and safe treatment with Phosphates Polyfusor." Alimentary pharmacology & therapeutics 17.10 (2003): 1325-1329 ("Terlevich") https://doi.org/10.1046/j.1365-2036.2003.01567.x
1010	Ogawa, T., Miyajima, M., Wakiyama, N. and Terada, K., 2013. Effects of phosphate buffer in parenteral drugs on particle formation from glass vials. Chemical and Pharmaceutical Bulletin, 61(5), pp.539-545. ("Ogawa") https://doi.org/10.1248/cpb.c12-01025
1011	U.S. Patent Application Publication No. 2019/0290602 ("Nevakar")
1012	RESERVED
1013	Nema, S. and Ludwig, J.D. eds., 2010. Pharmaceutical Dosage Forms: Parenteral Medications, Third Edition, Volume 1: Formulation and Packaging, 2010 Informa Healthcare, CRC Press. Chapters 5 and 12

Exhibit	Description
	ISBN-13: 9781420086430
1014	Rowe, Raymond C., Paul Sheskey, and Marian Quinn. "Handbook of Pharmaceutical excipients," pp. 637-40, 656-661 (2009) ISBN: 9781582121352
1015	ISMP Canada Safety Bulletin, Volume 6, Issue 2 April 25, 2006, Safety Strategies for Potassium Phosphates Injection https://web.archive.org/web/20061009113956/http://www.ismp-canada.org/download/ISMPCSB2006-02PotassiumPhosphates.pdf
1016	Litigation Docket and Statistics for Judge Williams, D. Del.
1017	Federal Drug Administration, NDA approval letter to CMP Development LLC, September 19, 2019 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/212121Orig1s000ltr.pdf
1018	Drug Administration, Orange Book, Prescription and Over-the-Counter Drug Product List, 39TH EDITION, Cumulative Supplement Number 09: September 2019, ADDITIONS/DELETIONS FOR PRESCRIPTION DRUG PRODUCT LIST https://web.archive.org/web/20191215034819/https://www.fda.gov/media/131880/download
1019	Brunelli, S.M. and Goldfarb, S., 2007. Hypophosphatemia: clinical consequences and management. Journal of the American Society of Nephrology, 18(7), pp.1999-2003.
1020	RESERVED
1021	Complaint, *Nivagen Pharma. Inc. v. Amneal Pharma. Inc.*, C.A. No. 24-846-GBW (D. Del.)
1022	Amended Complaint, *Nivagen Pharma. Inc. v. Amneal Pharma. Inc.*, C.A. No. 24-846-GBW (D. Del.)
1023	Declaration of Mina Ching from the Internet Archive (archive.org)
1024	Declaration of Dr. Sylvia Hall-Ellis, Ph.D.
1025	RESERVED

Exhibit	Description
1026	Wadsworth, R.L. and Siddiqui, S., 2016. Phosphate homeostasis in critical care. Bja Education, 16(9), pp.305-309.
1027	Pages 4-16 of Exhibit 1023, i.e., the September 23, 2020, Internet Archive of the WebSite https:/dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2c2078d1-9edc-4d0c-a72a-5491c28a5aac
1028	*Ex Parte Shirley*, Appeal No. 2009-2352, (B.P.A.I. May 14, 2009),
1029	Curriculum Vitae of Dr. Mansoor M. Amiji
1030	Perks, W., Iazzetta, J., Chan, P.C., Brouzas, A., Law, S. and Walker, S.E., 2017. Extended stability of sodium phosphate solutions in polyvinyl chloride bags. The Canadian Journal of Hospital Pharmacy, 70(1), p.7-12.
1031	U.S. Patent No. 4,872,553
1032	U.S. Patent No. 5,881,535
1033	U.S. Patent No. 5,896,989
1034	U.S. Patent No. 6,007,529
1035	U.S. Patent No. 6,713,137
1036	TechnoFlex Website: "PP bags for ready-to-use solution" Available from: https://web.archive.org/web/20180212220920/http:/www.technoflex.net/en/produit/pp-bags-for-ready-to-use-medication/
1037	U.S. Patent No. 5,783,269

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CLAIMS LISTING

Claim 1, Limitation 1.0	An isotonic sterile ready-to-use aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride,
Limitation 1.1	wherein the solution comprises 15 mmol/100 ml phosphorus and
Limitation 1.2	equal or less than 50 mcg/L aluminum.
Claim 3	The solution of claim 1, wherein the potassium is present in the solution in an amount of about 22 mEq/100 mL.
Claim 4	The solution of claim 1, wherein the sodium chloride is present in the solution in an amount of about 900 mg/100 ml.
Claim 5	The solution of claim 1, wherein the solution has a pH of between 6.2 and 6.8.
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 liquid particle count of no more than 360 and 30 for particles at 15 and 25 micrometer size, respectively.
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.
Claim 9	The solution of claim 1, wherein the solution is packaged in a flexible polyolefin container, optionally at a volume of 100 mL.
Claim 10	The solution of claim 9, wherein the flexible polyolefin container is further contained in a secondary metallized overwrap.
Claim 11, Limitation 1.0	A sterile ready-to-use premixed pharmaceutical product stored in a flexible polymeric container,
Limitation 11.1	wherein the pharmaceutical product comprises a potassium phosphates in an aqueous sodium chloride solution containing (a) less than 50 mcg/L aluminum,
Limitation 11.2	(b) about 15 mmol/100 ml phosphorus, and
Limitation 11.3	(c) about 22 mEq/100 mL potassium.

Claim 14	The pharmaceutical product of claim 11, wherein the premixed pharmaceutical product in the flexible polymeric container has a volume of 100 mL.
Claim 15	The pharmaceutical product of claim 11, wherein the flexible polymeric container is enclosed in a secondary metallized overwrap.
Claim 17, Limitation 17.0	A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising:
Limitation 17.1.A	administering, without prior dilution, an isotonic, sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container
Limitation 17.1.B	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;
Limitation 17.2	wherein the solution comprises about 15 mmol/100 ml phosphorus,
Limitation 17.3	about 22 mEq/100 mL potassium, and
Limitation 17.4	less than 50 mcg/L aluminum.
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.
Claim 19	The method of claim 17, wherein the route of administration is a central venous catheter.
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.

I. Introduction

Petitioner hereby seeks *inter partes* review of claims 1, 3-11, 14-15, and 17-20 (the "Challenged Claims") of U.S. Patent No. 11,813,291 (Ex-1001, "the '291 patent"). As shown below, the '291 patent relates to ready-to-use potassium phosphate solutions having low levels of aluminum. However, as shown herein, such solutions were already known in the art. Accordingly, all Challenged Claims should be cancelled.

II. Mandatory Notices Under 37 C.F.R. §42.8

A. Real Party-in-Interest Under 37 C.F.R. §42.8(b)(1)

Amneal Pharmaceuticals, Inc. ("Amneal") and its below listed affiliates/subsidiaries are the real parties-in-interest.

- Amneal EU, Ltd.
- Amneal Pharmaceuticals LLC
- Amneal Pharmaceuticals of New York, LLC
- Amneal Pharmaceuticals Pvt Ltd.

B. Related Matters Under 37 C.F.R. §42.8(b)(2)

The '291 patent is currently the subject of pending litigation: *Nivagen Pharma. Inc. v. Amneal Pharma. Inc.*, C.A. No. 24-846-GBW (D. Del.)("the Litigation"). (Exs. 1021-22.)

An *inter partes* review (IPR2025-00731) has also been filed against U.S. Patent No. 11,925,661 ("the '661 patent"), which is a child to the '291 patent.

The undersigned is unaware of any other matters involving the '291 patent that would affect, or be affected by, a decision in this IPR proceeding.

C. Lead and Back-up Counsel Under 37 C.F.R. §42.8(b)(3) and Service Information under 37 C.F.R. §42.8(b)(4)

Petitioner designates the following lead and back-up counsel:

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Service on Petitioner may be made by mail or hand delivery to: Greenberg Traurig, LLP, 1144 15th St., Suite 3300, Denver, CO 80202. Petitioner also consents to and prefers electronic service by emailing Amneal-IPRs@gtlaw.com and counsel of record.

III. Word Count

Petitioner certifies this Petition is 10,431 words, as counted by the word-processing program (Microsoft Word for Office 365) used to generate this Petition (excluding the table of contents, table of authorities, mandatory notices, certificate of service, and this certificate). This Petition complies with the 14,000 word limit (37 C.F.R. §42.24(a)(1)(i)).

IV. IPR Eligibility and Fees

Petitioner certifies under 37 C.F.R. §42.104(a) that the '291 patent is available for IPR and Petitioner is not barred or estopped from requesting cancellation of the Challenged Claims on the grounds identified below.

Ground	'291 Patent Claim	Basis
Ground 1	1, 3-9, 11, and 17-20	Rendered obvious by the CMP Art (Ex-1007 ("CMP-PCT"), Ex-1008/Ex-1027 ("CMP-FDA")) in view of Terlevich (Ex-1009) and Perks (Ex-1030), optionally in view of Ogawa (Ex-1010)
Ground 2	9-11, 14-15, and 17-20	Rendered obvious by the Ground 1 art in view of Nevakar (Ex-1011)

The IPR Petition fee and any necessary additional fees may be charged to Deposit Account No. 50-2638.

V. The '291 Patent

A. General Overview

The '291 patent generally relates to "ready-to-use (RTU) potassium phosphates in sodium chloride solution for phosphorus replacement therapy" having "potassium phosphate and sodium chloride at a fixed volume with 15 mmol/100 mL phosphorus and 22 mEq/100 mL potassium and less than 50 mcg/L aluminum." (Ex-1001 at Abstract.)

B. Priority Chain and Effective Filing Date

The '291 patent claims priority to provisional application no. 63/090,518 filed October 12, 2020. (Ex-1001 at (60).) Petitioner applies the October 12, 2020 date as the priority date without conceding that the '291 patent is entitled to such a priority date.

C. Prosecution History

The applications leading to the '291 patent and '661 patent both received first action allowances. (Ex-1002 at 146-153; Ex-1004 at 20-40.) In both instances, the Examiner argued Koneru (US11141430) was the closest prior art. (*Id.*)

D. The Challenged Claims

The Challenged Claims are 1, 3-11, 14-15, and 17-20; claims 1, 11, and 17 are independent.

VI. Discretionary Denial is Unwarranted

Pursuant to the PTAB's March 26, 2025 memorandum ("the Memo"), Petitioner does not include a full-blown *Fintiv* analysis, but Petitioner notes that discretionary denial is unwarranted.[1] The Litigation is in its infancy—a scheduling order has not yet been entered, discovery has not begun, infringement and invalidity contentions have not been exchanged, and a trial date has not been set. (Ex-1016 at 1-19 (the Litigation docket report).) Moreover, Judge Williams grants, on average, more than 70% of motions to stay pending IPR (Ex-1016 at 20), his average time to trial is 3 years (*id.* at 21), and he is currently setting trial dates for 2027, i.e., well after any FWD would issue in this proceeding. (Ex-1016 at 22-42 (October 9, 2024 order setting trial for May 10, 2027).) Furthermore, Petitioner hereby stipulates

[1] Per the Memo, Petitioner will provide its full discretionary denial analysis in response to Patent Owner's filing on the same.

under *Sotera* that, if this IPR is instituted, Petitioner will not pursue any grounds raised in this Petition, or any grounds Petitioner could have reasonably raised in this Petition, in the Litigation or any parallel proceeding. *Sotera Wireless, Inc. v. Masimo Corp.*, Case IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020). Accordingly, discretionary denial under §314(a) would be improper.

Non-institution under §325(d) would also be improper under the *Advanced Bionics* and *Becton Dickinson* factors. The only art cited against the claims of the '291 patent was US11141430, which is not included in any of Petitioner's Grounds. (*See* §V.C, *supra*.)

VII. Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSITA") in the field of the '291 patent as of October 12, 2020, would have had an advanced degree in chemistry, biology and/or pharmaceutics, 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. (Ex-1003-Amiji at ¶¶24-26.)

VIII. Claim Construction

Petitioner does not believe any claim constructions are required for purposes of this petition and interprets the claims at issue in accordance with their ordinary and customary meanings to the extent possible. 37 C.F.R. §42.100(b). Nonetheless, Petitioner is not suggesting that there are no disputes regarding claim scope,

including with respect to §112 issues. Rather, the Grounds raised herein anticipate or render obvious the Challenged Claims under any reasonable interpretation of the claims, and thus the Board need not issue any formal constructions. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co*., 868 F.3d 1013, 1017 (Fed. Cir. 2017).

IX. Prior Art Overview

A. Technology Background

1. Hypophospotemia Treatment By Intravenous Potassimum Phosphate Administration Was Well-Known As Were Ready-To-Use Solutions

As the Background of the ’291 patent admits, treatment of hypophospotemia by intravenous potassium phosphate administration was already well-known. (Ex-1001 at 1:34-2:28.) Indeed, in 2003, Terlevich provided “the largest published experience of the use of intravenous phosphate for the treatment of severe hypophosphataemia,” and concluded that “50 mmol phosphate [] over 24 h, is an effective treatment for refeeding syndrome, with 93% [] of cases achieving a serum phosphate concentration of > 0.50 mmol/L within 72 h.” (Ex-1009 at 1327.) A 2007 study found that “[u]se of a weight- and serum phosphate-based algorithm for intravenous phosphate repletion (Table 3) resulted in significant improvement in the proportion of patients who achieved normal serum phosphate” with the “bulk of existing evidence suggest[ing] the overall advantage of faster, more aggressive and tailored intravenous phosphate repletion regimens.” (Ex-1019 at 2002.) (*See also* Ex-1026 (article explaining hypophosphataemia causes and treatments, including

use of intravenous phosphate solutions).) Such parenteral solutions used combinations of monobasic potassium phosphate (KMP) and dibasic potassium phosphate (KDP).[2] (Ex-1026 at 309.) Hypophosphataemia patients also regularly received the ready-to-use (RTU) Phosphate Polyfusor® solution by Fresenius. (Ex-1009 at 1326 (explaining Phosphate Polyfusor® RTU solution/packaging), Ex-1026 at 309 ("A commonly used treatment is the Phosphate Polyfusor®…."); Ex-1003-Amiji at ¶¶41-43.)

2. Parenteral Potassium Phosphate Solutions Should Be Isotonic

It was also well-known that to "minimize tissue damage and irritation, reduce hemolysis of blood cells, and prevent electrolyte imbalance upon administration of small-volume parenterals, the product should be isotonic, or nearly so." (Ex-1013 at 100; *see also* Ex-1008 at 6; Ex-1027 at 8 (proper tonicity for potassium phosphate solutions must be used to avoid "vein irritation, vein damage, and/or thrombosis.").) Two commonly used tonicity agents are sodium chloride and dextrose. (Ex-1013 at 100 ("Sodium or potassium chloride and dextrose are commonly added to adjust

[2] For simplicity, Petitioner sometimes uses the common terms "KMP" and "KDP" to refer to monobasic potassium phosphate (KH_2PO_4 or "potassium hydrogen phosphate") and dibasic potassium phosphate (K_2HPO_4 or "potassium dihydrogen phosphate"), respectively. (Ex-1007 at 1:11-16; 11:18-20).)

hypotonic solutions."); Ex-1008 at 2; Ex-1027 at 4 (allowing for use of saline or dextrose with potassium phosphate solutions); Ex-1014 at 637 (explaining NaCl is "widely used in a variety of parenteral and nonparenteral pharmaceutical formulations, where the primary use is to produce isotonic solutions").) The most common use of sodium chloride in parenteral solutions is in the form of normal saline, which has a concentration of 0.9% NaCl (w/v) (0.9 g/100 ml). (Ex-1013 at 100 ("In isotonic solutions (e.g., 0.9% sodium chloride) the cells maintain their 'tone' and the solution is isotonic with human erythrocytes."); Ex-1008 at 2; Ex-1027 at 4 (disclosing to use 0.9% NaCl with potassium phosphate parenteral solutions); Ex-1010 at 540 (disclosing to use 0.9% NaCl as tonicity agent); Ex-1026 at 309 (disclosing to use 0.9% NaCl in KMP:KDP solutions); Ex-1030 at 7-8 (0.9% NaCl used with 15 mmol/100 ml phosphate solution); Ex-1003-Amiji at ¶¶47-50.)

3. Aluminum Issues Of Parenteral Solutions Were Well Known

Since at least 2011, it was known that parenteral solutions should avoid aluminum, which causes problems such as "fracturing osteomalacia and reduced bone mineralization, neurological dysfunction and dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis," leading the FDA to promulgate regulations "to minimize the amount of aluminum in parenteral products." (Ex-1007 at 1:27-2:13.) In glass vials, "aluminum continues to leach from the glass into the composition after storage for an extended period," which was known to cause

particulate precipitation at even ppb levels of aluminum, rendering the solution dangerous and unusable. (*Id.* at 19:8-9; Ex-1010 at 539 (explaining formation of insoluble particles leads to incidents, product recalls), 541 (explaining insoluble particles in patient's veins is unacceptable and "particle formation…should be completely prevented in the field of injectable drug products."), 544-45 (explaining low ppb Al requirement to avoid precipitate particles); Ex-1003-Amiji at ¶¶51-55.)

4. Ready-to-Use, Multilayer, Parenteral Containers Were Well Known

Some claims of the '291 patent require flexible plastic or polyolefin containers. Yet, the '291 patent examples merely employed conventional, off the shelf RTU containers, such as those produced by TechnoFlex, Grifols, HaemoPharm, and Informed Fluids. (Ex-1001 at 21:30-26:20, Table 20, "Bag Source"; Ex-1036.) The '291 patent does not purport to have invented new RTU containers, nor could it because ready-to-use, flexible, multiple layer plastic containers for parenteral administration were well known prior to the '291 patent:

> "With the development of plastic polymer technology ***over the last 30 years***, plastics have become logical alternatives for small-volume parenteral (SVP) and large volume parenteral (LVP) packaging." (Ex-1013 at 305.)

Indeed, for decades, numerous medical-grade, RTU flexible containers have been described. (*See* Exs. 1031-1037.) Thus, prior to the '291 patent, a POSITA knew it

was conventional to store intravenous and other ready-to-use solutions in flexible multilayer containers. (Ex-1003-Amiji at ¶¶56-57.)

A POSITA also knew to avoid PVC (polyvinyl chloride) RTU containers because PVC allows water evaporation and has phthalate leaching issues. (Ex-1003-Amiji at ¶58; Ex-1030; Ex-1013 at 309; Ex-1031 at 1:48-55; Ex-1037 at 1:5-30.) Instead, a POSITA would have used well-known water impermeable materials, such as multiple layers of polyolefins, which were known to restrict or avoid evaporation during long term storage:

> "Multilayer plastics: Plastic bags ***commonly*** used for LVP generally ***consist of between three and five layers of plastic film consisting of two or more different resins***….The purpose is to produce a plastic film that combines the best properties of each film including good clarity, excellent flexibility and durability, ***which also is a strong barrier to water vapor transmission***." (Ex-1013 at 309.)
>
> "Multilayer bags are typically used and are intended to maintain product integrity. These bags provide gas and moisture barrier properties, functionality after sterilization, durability and biocompatibility (Table 4)." (*Id.* at 319.)

(Ex-1003-Amiji at ¶58, *see also* Ex-1031 at 2:40-49, 4:23-36; Ex-1033 at 3:66-4:1; Ex-1034 at 3:36-47, 7:26-31, and 8:43-55; Ex-1035 at 1:46-2:67.)

B. Applicant Admitted Prior Art ("AAPA")

The '291 patent includes the following pertinent AAPA:

- "Phosphorus replacement therapy is generally administered via. peripheral venous catheter or central venous catheter and at a rate according to the maximum recommended concentration and infusion rate as is shown in Table 1 (Maximum Recommended Daily Concentration of Potassium Phosphates Injection By Age and Route of Administration (Peripheral vs. Central)) and Table 2 (Maximum Recommended Infusion Rate of Potassium Phosphates Injection For Adults and Pediatric Patients 12 Years of Age and Older)"[3] (Ex-1001 at 1:43-53)

C. The CMP Art (Exs. 1007-08, 1027)

The CMP Art includes a CMP DEV LLC ("CMP") international (PCT) patent application to parenteral phosphate solutions (Ex-1007, "CMP-PCT") and an FDA Drug Label issued to CMP specific to those solutions ("CMP-FDA"). (Ex-1003-Amiji at ¶68.)

Specifically, "CMP-PCT" is International Publication No. WO2020/081118 to CMP published April 23, 2020, i.e., prior to the effective filing date of the '291 patent, and is thus AIA §102(a)(1) prior art. CMP-PCT discloses "a sterile composition for injection comprised of potassium phosphates having no visible

[3] The Background disclaimer is ineffective. *Ex Parte* Shirley, Appeal No. 2009-2352, (B.P.A.I. May 14, 2009), pp.17-26 (disclaimers ineffective if the disclosures are prior art). (Ex-1028.)

particulate" and "a manufacturing process for the sterile composition and its use." (Ex-1007 at 1:7-9.) CMP-PCT is analogous art to the '291 patent. (Ex-1003-Amiji at ¶¶69-71).[4]

CMP-FDA is an FDA Drug Label likely published in September 2019 (Ex-1008), and certainly no later than September 23, 2020 (Ex-1027). (Ex-1003-Amiji at ¶¶72, 82-91; Ex-1023 at 4-16; Ex-1027.) CMP-FDA is prior art under at least AIA §102(a)(1). CMP-FDA is analogous art to the '291 patent. (Ex-1003-Amiji at ¶73.) CMP-FDA provides additional details surrounding the parenteral solutions described by CMP-PCT including an adjustment of tonicity using 0.9% sodium chloride and administration by a peripheral or central venous catheter. (Ex-1003-Amiji at ¶74; *id.* at ¶¶75-81, tying FDA documents (Exs. 1008, 1017-18, 1023, 1027) to CMP-PCT.)

D. Terlevich (Ex-1009)

Terlevich is a journal article published in 2003. (Ex-1024 at ¶¶48-56, 105.) Terlevich is at least AIA §102(a)(1) prior art. Terlevich is analogous art to the '291 patent. (Ex-1003-Amiji at ¶¶92-93.) Terlevich discloses "hypophosphataemia associated with refeeding syndrome requires treatment with intravenous phosphate

[4] The '291 patent cites the U.S. version of CMP-PCT. (Ex-1001 at 2:47-52.) The Examiner did not cite CMP-PCT against the claims of the '291 patent.

to prevent potentially life-threatening complications," and that it has administered "aliquots of intravenous phosphate to correct hypophosphataemia" using "50 mmol of intravenous phosphate, infused over 24 h via a dedicated peripheral intravenous cannula," which was "conveniently given as a 'Phosphates Polyfusor' (PPF) (Fresenius Kabi Ltd., Warrington, UK)." (Ex-1009 at 1325-26.) The Fresenius "Polyfusor is a sealed semi-rigid cylindrical polyethylene container, with a twist-off seal at one end and a ring tab at the other." A "500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium." (*Id.* at 1326; Ex-1003-Amiji at ¶94.)

E. Ogawa (Ex-1010)

Ogawa is a journal article published in 2013 and is AIA §102(a)(1) prior art. (Ex-1024 at ¶¶57-65. 105.) Ogawa is analogous art to the '291 patent. (Ex-1003-Amiji at ¶¶95-96.) Ogawa conducted studies that showed less than 50 ppb of aluminum should be used in parenteral phosphate solutions to avoid particle formation. (Ex-1010 at 544-45; Ex-1003-Amiji at ¶97.)

F. Perks (Ex-1030)

Perks is a journal article published in 2017 and is AIA §102(a)(1) prior art. (Ex-1024 at ¶¶96-105.) Perks is analogous art to the '291 patent. (Ex-1003-Amiji at ¶¶118-19.) Perks conducted studies on phosphate solutions having 15 mmol/100 ml phosphate in PVC bags. (Ex-1030 at 7 (Objective); Ex-1003-Amiji at ¶120.)

G. Nevakar (Ex-1011)

Nevakar is U.S. Patent Application Publication No. 2019/0290602 published September 26, 2019 and is AIA §102(a)(1) prior art. Nevakar is analogous art to the '291 patent. (Ex-1003-Amiji at ¶¶98-99.) Nevakar discloses that "storage stable ready-to-administer composition[s]" may be packaged in a "flexible IV bag" "between 100 mL and 1,000 mL, and may be further enclosed in a metallized over-container" such as an "an aluminum foil pouch or single- or multi-layer overwrap." (Ex-1011 at 0011, 0015, 0029; Ex-1003-Amiji at ¶100.)

X. Ground 1: Claims 1, 3-9, 11, and 17-20 are obvious in view of the CMP Art, Terlevich, and Perks, optionally in view of Ogawa

A. Scope, Content and Motivation to Combine

For Ground 1, the prior art is the CMP Art (Exs. 1007-08, 1027), Terlevich (Ex-1009), and Perks (Ex-1030), optionally in view of Ogawa (Ex-1010). (Ex-1003-Amiji at ¶¶123-27.)

CMP-PCT (Ex-1007) discloses a "sterile composition for injection comprised of potassium phosphates having no visible particulate" and "a manufacturing process for the sterile composition and its use." (Ex-1007 at Abstract.) Like the '291 patent, the compositions are used to treat "hypophosphatemia in a patient in need thereof." (*Id.* at 4:23-25; Ex-1003-Amiji at ¶¶128-30.)

As CMP-PCT explains, prior to its alleged invention, a prior potassium phosphates solution contained 224 mg of KMP and 236 mg of KDP per milliliter of

solution. (Ex-1007 at 1:11-16.) However, this solution was prone to particulate issues, and thus the CMP-PCT "inventors sought to solve the visible particulate problem," which the inventors did by adjusting the amounts of KMP and KDP:

> "After a detailed investigation, it was determined that the aforementioned problems are solved by a sterile composition for injection, comprising: (a) about 175 mg/mL [KMP]; (b) about 300 mg/mL [KDP]; and (c) a sufficient amount of a water vehicle; wherein the total amount of phosphate is about 3 mmol/mL." (*Id.* at 2:15-24.)

The CMP-PCT composition had "no visible particles after storage at about 25°C and 60% relative humidity for 3-months…24-months, or longer." (*Id.* at 3:13-21; Ex-1003-Amiji at ¶¶131-32.)

CMP-PCT does not disclose that its solutions are ready-to-use (RTU). Instead, 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. (*Id.* at 4:25-27.) Nonetheless, it was obvious to premix and provide the CMP-PCT solutions as ready-to-use solutions. (Ex-1003-Amiji at ¶¶133-34.)

Specifically, like CMP-PCT and the '291 patent, Terlevich discloses the treatment of "hypophosphataemia associated with refeeding syndrome…with intravenous phosphate to prevent potentially life-threatening complications." (Ex-

1009 at 1325.) Terlevich further teaches that while he had previously used "aliquots of intravenous phosphate to correct hypophosphataemia," "[t]he initial administration of 5–10 mmol, repeated as required, *was inadequate*, and most patients ultimately required 50 mmol over 24 h with no adverse events." (*Id.* at 1326.) Accordingly, Terlevich switched to a ready-to-use solution for convenience and efficacy:

> "Thus, *we **now*** use 50 mmol of intravenous phosphate, infused over 24 h via a dedicated peripheral intravenous cannula, in all refeeding syndrome patients except those in renal failure. **This** can be *conveniently* given as a 'Phosphates Polyfusor' (PPF) (Fresenius Kabi Ltd., Warrington, UK). *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. A 500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium*." (*Id.* at 1326.)
>
> "Our study demonstrates that 50 mmol phosphate, given as a PPF over 24 h, is an effective treatment for refeeding syndrome, with 93% (28) of cases achieving a serum phosphate concentration of > 0.50 mmol/L within 72 h." (*Id.* at 1327.)

A POSITA would have recognized that Terlevich's "Phosphates Polyfusor" is a RTU solution because it is in a "sealed semi-rigid cylindrical polyethylene container with a twist-off seal at one end and a ring tab at the other," and has a suitable phosphate concentration (10 mmol/100 ml) for direct administration to the patient without dilution. (Ex-1003-Amiji at ¶¶135-36; Ex-1026 at 309.) Further, Perks

teaches that diluted phosphate solutions for treatment of hyperphosphatemia commonly contain from 3 mmol/100 ml to 15 mmol/100 ml of phosphate:

> "Concentrated sodium phosphate injection provides 4 mmol/mL and 3 mmol/mL of sodium and phosphate, respectively. At this concentration, *the solution must be sufficiently diluted*, thoroughly mixed, and infused at an appropriate rate to prevent phlebitis, hypernatremia, hyperphosphatemia, and changes to calcium metabolism. As a result, many hospital pharmacies have been preparing ***dilute sodium phosphate solutions, typically in the range of 30 to 150 mmol/L of phosphate***." (Ex-1030 at 8.)[5]

(Ex-1003-Amiji at ¶137.)

A POSITA would have been motivated to apply the teachings of Terlevich and Perks to CMP-PCT. All references are directed to treating hypophosphatemia with phosphate solutions, with CMP-PCT disclosing concentrated solutions for later dilution, Terlevich disclosing RTU solutions having 10 mmol/100 ml phosphate, and Perks teaching "*many hospital pharmacies* have been preparing *dilute sodium phosphate solutions,* ***typically in the range of 30 to 150 mmol/L of phosphate***,"

[5] A concentration of 30 mmol/L of phosphate is 3 mmol/100 ml of phosphate, and a concentration of 150 mmol/L of phosphate is 15 mmol/100 ml of phosphate. (Ex-1003-Amiji at ¶137, N.4.)

which encompasses the 10 mmol/100 ml phosphate range taught by Terlevich. (Ex-1003-Amiji at ¶138.)

Further, as Terlevich explains, RTU solutions are easier to administer over a 24-hour period than aliquots of diluted solutions. A POSITA would have appreciated the ease and use of a RTU solution, which allows for direct administration by a practitioner and without the need to dilute a prior solution. (Ex-1013 at 317-18 (explaining benefits of premixed packaging).) A RTU solution also helps avoid unnecessary calculations, and potential errors, by practitioners. (Ex-1015 at 1 ("A variety of measurement units (mg, mEq, mmol, mOsm, mL) are used on the labels. The variety of information may cause confusion and may lead to calculation errors during preparation of doses for intravenous infusion.").) Accordingly, a POSITA would have been motivated to produce the CMP-PCT solutions as RTU solutions based on the teachings of Terlevich and with a phosphate concentration of anywhere from 3 mmol/100 ml to 15 mmol/100 ml as taught by Perks. (Ex-1003-Amiji at ¶¶138-40.)

A POSITA also would have had a reasonable expectation of success. Ready-to-use solutions potassium phosphate solutions were already known, and it would be straightforward to apply the teachings of Terlevich and Perks to CMP-PCT to achieve RTU solutions. (Ex-1003-Amiji at ¶141.)

Specifically, it was obvious to prepare the CMP-PCT solutions as RTU solutions having a phosphate concentration of anywhere from 3 mmol/100 ml to 15 mmol/100 ml as taught by Perks while keeping the relative amounts of KMP and KDP the same. Doing so would reasonably be expected to maintain CMP's goal of no particulates while also realizing a RTU solution for administration. Accordingly, it was obvious based on Perks and Terlevich to prepare a RTU potassium phosphate solution having 15 mmol/100 ml of phosphate. (Ex-1003-Amiji at ¶142.)

In preparing a 15 mmol/100 ml phosphate RTU solution, a POSITA would note that CMP-PCT discloses a total phosphate concentration of 3 mmol/ml or 300 mmol/100 ml, which is 20 times higher than the 15 mmol/100 ml phosphate concentration of Perks. (Ex-1007 at 2:29-32; Ex-1030 at 8.) A POSITA would, therefore, find it obvious to decrease the KMP and KDP levels in the CMP-PCT solutions by a factor of 20 when preparing RTU solutions. A POSITA would not expect any change in particulate levels in such RTU solutions because (a) the relative amounts of KMP and KDP are maintained, (b) CMP-PCT specifies the use of ultra-low levels of aluminum, which avoids precipitation of phosphate particles, and (c) CMP-PCT teaches that particulate generation in plastic vials is not an issue. (Ex-1003-Amiji at ¶¶143-49; Ex-1007 at 13:32-17:8 (examples showing lowered level of KMP prevents particulate precipitation while maintaining total phosphate concentration at 3 mmol phosphate/ml), 18:24-19:5 (examples showing no

particulates due to KMP+KDP concentration), 19:6-29 (explaining low levels of aluminum should be used), 20:5-7 ("Based on these results, it is contemplated that [the] composition stored in a plastic vial may be stored at room temperature").)

Based on the teachings of CMP-PCT, Terlevich and Perks, a POSITA would use the below amounts of KMP and KDP in a RTU solution.

- CMP-PCT teaches the use 175 mg/ml of KMP or 17,500 mg/100 ml; divide by 20 to achieve target RTU concentration (per Perks), which results in about 875 mg/100 ml or 6.42 mmol/100 ml of KMP. (The molecular weight of KMP is 136.09 g/mol.)
- CMP-PCT teaches the use of 300 mg/ml of KDP or 30,000 mg/100 ml; divide by 20 to achieve target RTU concentration (per Perks), which results in 1500 mg/100 ml or 8.61 mmol/100 ml of KDP. (The molecular weight of KDP is 174.18 g/mol.)

(Ex-1003-Amiji at ¶150.) Thus, a POSITA seeking to produce a RTU solution based on the teachings of CMP-PCT, Terlevich and Perks would have found it obvious to produce a solution having 6.42 mmol/100 ml KMP and 8.61 mmol/100 ml KDP for a total phosphate concentration of about 15 (15.03) mmol/100 ml and to store such RTU solutions in a suitable pharmaceutical grade plastic container as taught by Terlevich. (*Id.* at ¶151.)

CMP-PCT does not specifically disclose the use of 900 mg /100 ml (0.9%) sodium chloride (saline) in its solutions. However, CMP-PCT teaches that its diluted solutions should contain dextrose, which is a common tonicity agent. (Ex-1007 at 4:28-30.) Another common tonicity agent is saline, and a POSITA would have been motivated to include 0.9% NaCl (saline) in the ready-to-use solutions taught by the combination of CMP-PCT, Terlevich and Perks. (Ex-1003-Amiji at ¶152.) Indeed, it was well-known that both dextrose and sodium chloride are commonly used in parenteral pharmaceutical formulations to produce isotonic solutions. (§IX.A.2, *supra*; Ex-1013 at 100; Ex-1014 at 637; Ex-1010 at 540; Ex-1026 at 309.)

Furthermore, the *exact* solution disclosed by CMP-PCT was approved for use by the FDA in 2019. (Ex-1003-Amiji at ¶¶75-81, 153; Ex-1017 (FDA approval letter for CMP); Ex-1018 (October 2019 Orange Book Cumulative Supplement) at 21 listing "CMP DEV LLC" as having approval for potassium phosphate solutions having 300 mg/ml KDP and 175 mg/ml KMP.) Notably, the Orange Book approved KDP and KMP amounts are *identical* to the concentrations disclosed by CMP-PCT. (Compare Ex-1007 at 2:29-32 to Ex-1018 at 21.) Thus, a POSITA would have known the FDA approved the 300 mg/ml KDP plus 175 mg/ml KMP solutions described in Ex-1007 for public use in 2019. (Ex-1003-Amiji at ¶¶75-81.)

The FDA Drug Label corresponding to the Orange Book approved CMP-PCT solution is included as Ex-1008 and Ex-1027 ("CMP-FDA"), and this FDA label

expressly calls for the use of 0.9% NaCl with diluted CMP solutions. (Ex-1008 at 2; Ex-1027 at 4 ("Using aseptic technique, withdraw the required dose from the vial and add to 100 mL to 250 mL of 0.9% Sodium Chloride Injection, USP (normal saline)").).[6] A POSITA would seek to comply with the FDA specifications for diluted CMP solutions, and thus would have been motivated to use 0.9% NaCl in the RTU solutions taught by the combination of CMP-PCT, Terlevich and Perks. Perks confirms that 0.9% NaCl should be used with a 15 mmol/100 ml potassium phosphate solution. (Ex-1030 at 8 ("The objective of this study was to evaluate the physical compatibility and chemical stability of 30 mmol/L phosphate and 150 mmol/L phosphate in 5% dextrose in water (D5W) ***or 0.9% sodium chloride (normal saline [NS])*** stored in PVC bags at both room temperature (23°C) and 4°C for 63 days.").) (Ex-1003-Amiji at ¶153.)

A POSITA also would have had a reasonable expectation of using 0.9% NaCl in a RTU solution as it was commonplace to use 0.9% NaCl as a tonicity agent, and the FDA even requires 0.9% NaCl in the diluted CMP solutions, showing a POSITA

[6] CMP-FDA also includes the exact phosphate solutions disclosed by CMP-PCT. (Ex-1008 at 9; Ex-1027 at 10 ("Each mL contains 175 mg of [KMP] and 300 mg of [KDP].").)

is readily capable of producing CMP's solutions with 0.9% NaCl. (§IX.A.2, *supra*; Ex-1003-Amiji at ¶154; Exs. 1008, 1010, 1013-14, 1026-27, 1030.)

For at least the above reasons, a POSITA would have been motivated to combine the teachings of the CMP Art, Terelivch and Perks to provide a RTU potassium phosphate solution having (a) 15 mmol/100 ml phosphate (by including 6.42 mmol/100 ml (875 mg/100 ml) of KMP and 8.61 mmol/100 ml (1500 mg/100 ml) of KDP in solution), and (b) 0.9% NaCl (900 mg/100 ml) with a reasonable expectation of success. (Ex-1003-Amiji at ¶155.)

Finally, CMP-PCT teaches to use ultra-low levels of aluminum (≤1 ppm), with its experimental solutions realizing 0.2-0.3 ppm Al after extended periods in a plastic container. (Ex-1007 at 4:4-15 ("an aluminum content of not more than…about 1 ppm after storage at 4-8°C [or room temperature] for…36-months, or longer…"); 20:1-7 ("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***").) These CMP-PCT teachings alone render obvious the aluminum requirement of the '291 patent's claims (≤0.50 mcg/L), which requirement is arbitrary given the '291 patent allows for up to 4.2 ppm of Al in its solution production materials (4200 mcg/L Al), which is even higher than the "not more than about 1 ppm" requirement of CMP-PCT. (Ex-1003-Amiji at ¶156; Ex-1001 at

Tables 5-7 (showing Al allowed content of KMP, KDP, and NaCl totals 4.2 ppm); Ex-1005 at 16 (showing 518-PRV claimed up to 100 mcg/L Al).)

Nonetheless, a POSITA would have been motivated to include as little as aluminum as possible. As explained in §IX.A.3, it was well-known that aluminum is toxic and also causes particle precipitation in parenteral solutions. (Ex-1007 at 1:27-2:13; Ex-1010 at 544-45.) Indeed, Ogawa tested several phosphate buffer solutions and found that even as little as 50 ppb of aluminum may cause particle precipitation:

> "As shown in Table 4, both the phosphate buffer without additional Al ions and *the phosphate buffer containing* ***25 ppb of added Al ions did not*** *form particles, even after 25 weeks in storage.* ***In contrast, the addition of 50 ppb*** *or more of Al produced white particles*. … [T]hese results also suggest that the addition of 50 ppb of Al ions in phosphate buffer solution has the ability to form a detectable amount of particles for this study condition. The reason why these particles have different morphologies is thought to be due to difference in increasing rate of Al ion in the solution." (Ex-1010 at 544.)

Ogawa also recognized that particles need to be *completely* eliminated in phosphate parenteral solutions. (Ex-1010 at 541 ("Al-phosphate complex formation in other injectable drugs is unacceptable because these insoluble particles have the ability to harm the patient's veins….Therefore, the phenomenon of particle formation from the storage of phosphate buffer solution in glass vials induced by interactions of the

phosphate ions with Al eluted from the vial *should be completely prevented in the field of injectable drug products*.").) Further, both CMP-PCT and Ogawa recognize that borosilicate glass may cause increasing aluminum content in parenteral solutions over time. (Ex-1007 at 19:8-9; Ex-1010 at 540 ("it is empirically known that phosphate buffer is incompatible with glass vials and that particles are formed"), 541 ("It is suggested that the particles were formed as a result of interactions between eluted Al ions from the surface of the glass vials and the phosphate ions in the solution.").) (Ex-1003-Amiji at ¶¶157-59.)

CMP-PCT desires to have no particles and ≤1 ppm aluminum in solution after an extended period. (Ex-1007 at 3:22-27, 4:4-15.) A POSITA would have been motivated to apply Ogawa's aluminum teachings to CMP-PCT to ensure that the CMP-PCT solutions avoided any particle formation over an extended period of time. A POSITA also would have been motivated to use plastic containers, avoiding glass containers, as expressly taught by CMP-PCT. (Ex-1003-Amiji at ¶160; Ex-1007 at 20:1-7.)

A POSITA also would have had a reasonable expectation of success in applying Ogawa's teachings. CMP-PCT teaches to use plastic containers to avoid aluminum leaching issues associated with glass vials. (Ex-1007 at 19:8-9, 20:1-7.) Further, a POSITA would reasonably expect to achieve <50 ppb of aluminum, per Ogawa, by using pharmaceutical grade or ultra-pure KMP, KDP, and NaCl starting

materials. (Ex-1014 at 637-38, Table II (providing specification for NaCl of <0.2 ppm Al) and 656-661 (providing sodium/potassium monobasic/dibasic specifications with ultra-low levels of metals).) Indeed, CMP-PCT already achieved 200-300 ppb Al levels, which are very close to 50 ppb, and it would be routine to test for <50 ppb Al in the CMP-PCT solutions given both CMP-PCT and Ogawa already tested for those levels. Thus, a POSITA would have reasonably expected to achieve <50 ppb Al in the CMP-PCT solutions. (Ex-1003-Amiji at ¶161.)

B. The CMP Art, Terlevich and Perks, optionally in view of Ogawa, Render Obvious Claims 1-9, 11-13, and 17-20

[Claim 1, 1.0] An isotonic sterile ready-to-use aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride, …

The CMP Art in view of Terlevich teaches this limitation.

CMP-PCT teaches sterile potassium solutions comprising potassium phosphates:

> "A first embodiment is directed to a *sterile* composition for injection, comprising: (a) about 175 mg/mL *potassium monobasic phosphate*; (b) about 300 mg/mL of *potassium dibasic phosphate*; and (c) a sufficient amount of a water vehicle; wherein the total amount of phosphate is about 3 mmol/mL." (Ex-1007 at 2:29-32.)[7]

[7] The "first and second embodiments" described by CMP relate to solutions having 175 mg/mL KMP and 300 mg/mL KDP, while the third and fourth embodiments

Further, as explained in §X.A, *supra*, CMP-PCT does not disclose that its solutions are ready-to-use (RTU) because they are diluted "with a pharmaceutically acceptable diluent to obtain a diluted composition," which diluted solutions are then intravenously administered to the patient. (*Id.* at 4:25-27.) Nonetheless, as explained in §X.A, Terlevich discloses ready-to-use potassium phosphate solutions:

> "Thus, *we* ***now*** use 50 mmol of intravenous phosphate, infused over 24 h via a dedicated peripheral intravenous cannula, in all refeeding syndrome patients except those in renal failure. **This** can be *conveniently* given as a 'Phosphates Polyfusor' (PPF) (Fresenius Kabi Ltd., Warrington, UK). *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. A 500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium*." (Ex-1009 at 1326.)

As also explained above, it obvious in view of Terlevich to produce the CMP-PCT solutions as RTU solutions with a reasonable expectation of success. Thus, CMP-PCT in view of Terlevich teaches "sterile ready-to-use aqueous potassium solution, comprising potassium phosphates." (Ex-1003-Amiji at ¶¶162-65.)

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described by CMP relate to KMP only solutions. (Ex-1007 at 2:29-3:4; 7:18-25; Ex-1003-Amiji at ¶129.)

Further, as explained in §§IX.A.2 and X.A, the use of saline as a tonicity agent to provide isotonic potassium phosphate solutions was well-known, and even mandated by the FDA when employing diluted CMP-PCT solutions:

> "Preparation
>
> - POTASSIUM PHOSPHATES INJECTION is for intravenous infusion into a central or peripheral vein only after dilution.
> - Using aseptic technique, withdraw the required dose from the vial and add to 100 mL to 250 mL *of 0.9% Sodium Chloride Injection, USP (normal saline)* or 5% Dextrose Injection, USP (D5W)." (Ex-1008 at 2; Ex-1027 at 4.)

CMP-FDA teaches to prepare isotonic solutions by avoiding hypertonic solutions:

> "POTASSIUM PHOSPHATES INJECTION ***must be*** diluted and ***administered in intravenous fluids*** or used as an admixture in parenteral nutrition. ***It is not for direct intravenous infusion***. ***The infusion of hypertonic solutions into a peripheral vein may result in*** vein irritation, vein damage, and/or thrombosis. The primary complication of peripheral administration is venous thrombophlebitis,which manifests as pain, erythema, tenderness or a palpable cord. Remove the catheter as soon as possible and initiate appropriate medical treatment if thrombophlebitis develops." (Ex-1008 at 6; Ex-1027 at 8.)

Thus, the CMP Art in view of Terlevich teaches this limitation. (Ex-1003-Amiji at ¶¶166-68.)

[1.1] wherein the solution comprises 15 mmol/100 ml phosphorus and

CMP-PCT in view of Terlevich and Perks teaches this limitation. Specifically, CMP-PCT teaches undiluted solutions having 3 mmol/ml phosphate (300 mmol/100 ml). (Ex-1007 at 2:29-32 ("wherein the total amount of phosphate is about 3 mmol/mL").) As explained in §X.A, it was obvious in view of Terlevich and Perks to produce the CMP-PCT solutions as RTU solutions having a total phosphate concentration of 15 mmol/100 ml (150 mmol/L), which was a typical concentration used by hospital pharmacies for the treatment of hyperphosphatemia:

> "Concentrated sodium phosphate injection provides 4 mmol/mL and 3 mmol/mL of sodium and phosphate, respectively. At this concentration, *the solution must be sufficiently diluted*, thoroughly mixed, and infused at an appropriate rate to prevent phlebitis, hypernatremia, *hyperphosphatemia*, and changes to calcium metabolism. As a result, *many hospital pharmacies* have been preparing ***dilute sodium phosphate solutions, typically in the range of 30 to 150 mmol/L of phosphate***." (Ex-1030 at 8.)

As shown, Perks acknowledges the same starting concentration as CMP-PCT ("3 mmol/ml phosphate") and teaches to dilute it to 15 mmol/100 ml for administration for a patient condition, including hyperphosphatemia. Thus, it was obvious to a POSITA to dilute the CMP-PCT solutions to 15 mmol/100 ml in view of Perks for use as an RTU solution as taught by Terlevich.

Accordingly, CMP-PCT in view of Terlevich and Perks teaches this limitation. (Ex-1003-Amiji at ¶¶169-71.)

[1.2] equal or less than 50 mcg/L aluminum.

CMP-PCT teaches this limitation, optionally in view of Ogawa. Specifically, CMP-PCT teaches to use ≤ 1ppm Al, with its example solutions realizing as little as 0.2 ppm Al:

> "[A]n aluminum content of not more than…about 1 ppm after storage at 4-8°C [or room temperature] for…36-months, or longer." (Ex-1007 at 4:4-15.)
>
> "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. Based on these results, it is contemplated that [the] composition stored in a plastic vial may be stored at room temperature." (*Id.* at 20:1-7.)

A concentration of 0.2-0.3 ppm Al corresponds to a range of 200-300 mcg/L of Al, which is very close to, and renders obvious, the claimed range of 50 mcg/L Al. (Ex-1003-Amiji at ¶¶156, 173-75; *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985)(prior art alloy so close to claim that *prima facie* case of obviousness was established).) Indeed, a POSITA would not have expected any material difference between a potassium phosphate buffer solution having 50 ppb or 200 ppb Al because both concentrations would tend to promote generation of

insoluble particulate particles, as Ogawa shows. Thus, CMP-PCT alone renders obvious this limitation. (Ex-1003-Amiji at ¶¶172-76.)

Limitation [1.2] is also taught by CMP-PCT in view of Ogawa. As explained in §X.A, based on Ogawa, a POSITA would have been motivated to use <50 ppb Al in parenteral phosphate buffer solutions (e.g., the CMP-PCT solutions), preferably 25 ppb Al or less, to avoid particle formation, and a POSITA would have had a reasonable expectation of successfully doing so. (<50 ppb Al corresponds to <50 mcg/L.[8]) Thus, CMP-PCT in view of Ogawa also teaches this limitation. (Ex-1003-Amiji at ¶¶177-78.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, teaches all limitations of and renders obvious claim 1. (Ex-1003-Amiji at ¶179.)

[Claim 3] The solution of claim 1, wherein the potassium is present in the solution in an amount of about 22 mEq/100 mL.

CMP-PCT in view of Terlevich and Perks teaches this limitation.

First, "about 22 mEq" reads on solutions having +/- 5% of this amount, i.e., up to 23.1 mEq/100 ml because the '291 patent provides for a "Release

[8] As Dr. Amiji explains, 1 ppm equals 1,000 mcg/L, i.e., 1 ppb = 1 mcg/L. (Ex-1003-Amiji at ¶64.)

Specification" of from 95.0% to 105.0% of the target potassium concentration, as shown in Table 8:

TABLE 8

Specification of Potassium Phosphates in Sodium Chloride Injection, RTU

Sr. No.	Test	Release Specification	Shelf Life Specification	Reference
***				
7.	Container content for Injections	Not less than 100.0 mL	Not less than 100.0 mL	USP <697>
8.	Assay of Potassium (Label Claim: Each 100 mL bag contains 8.50 mg/mL of Potassium	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
9.	Assay of Phosphorus (Label Claim: Each 100 mL bag contains 4.65 mg/mL of Phosphorus)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
10.	Assay of Sodium (Label Claim: Each 100 mL bag contains 3.57 mg/mL of Sodium)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house

(Ex-1001 at Table 8 (annotations added).) (Ex-1003-Amiji at ¶¶180-81.)

Second, CMP-PCT teaches its undiluted solutions include "about 4.7 mEq/mL" or 470 mEq per 100 mL potassium. (Ex-1007 at 17:1-8.) As explained in §X.A, it was obvious based on the teachings of CMP-PCT and Perks to produce a RTU CMP solution diluted by a factor of 20. Thus, CMP-PCT in view of Perks teaches a solution having "about 23.5 mEq" of potassium (470/20=23.5) per 100 ml of solution, which is indistinct from a solution having "23.1 mEq/100 mL" as allowed by the "about" language of the claims. Indeed, a POSITA would expect no material difference between a solution having 23.1 mEq/100 ml and that having 23.5

mEq/100 ml as both would be well under maximum initial or single dose allowances, as CMP-FDA expressly shows:

> "The phosphorus doses in Table 1 are general recommendations for an initial or single dose and are intended for most patients. Based upon clinical requirements, some patients may require a lower or higher dose. *The maximum initial or single dose of phosphorus is 45 mmol* ***(potassium 71 mEq)*** [see Warnings and Precautions (5.1)]" (Ex-1008 at 3; Ex-1027 at 5.)

Thus, claim 3 is obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶¶182-83.)

[Claim 4] The solution of claim 1, wherein the sodium chloride is present in the solution in an amount of up to 900 mg/100 ml.

The CMP Art in view of Terlevich and Perks teaches this limitation.

Specifically, as shown in §§IX.A.2 and X.A, it was conventional to use 900 mg/100 ml of sodium chloride, commonly known as normal saline, in intravenously administered phosphate solutions. Moreover, CMP-FDA requires 900 mg/100 ml of saline in diluted CMP solutions and Perks teaches the use of 900 mg/100 ml saline for 15 mmol/100 ml potassium phosphate solutions. (Ex-1008 at 2; Ex-1027 at 4; Ex-1030 at 8.) (Ex-1003-Amiji at ¶¶184-85.)

Thus, claim 4 is obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶186.)

[Claim 5] The solution of claim 1, wherein the solution has a pH of between 6.2 and 6.8.

CMP-PCT teaches this limitation. Specifically, CMP-PCT teaches its solutions have pH of about 6.5 to about 7.5, which overlaps the claimed range. (Ex-1007 at 3:7-8 ("the composition has a pH of about 6.5 to about 7.5….").) The use of 0.9% NaCl in the RTU solutions taught by the combination of the CMP Art, Terlevich and Perks would not materially impact the pH, i.e., a pH of about 6.5-7.5 would still reasonably be expected when using 0.9% NaCl as taught by CMP-FDA at least because 0.9% NaCl has a pH of about 5.5, so its use in the CMP potassium phosphates solution would, if anything, slightly shift the pH downward, overlapping even further with the claimed range. (Ex-1003-Amiji at ¶¶187-88.)

Thus, claim 5 is obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶¶189.)

[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 liquid particle count of no more than 360 and 30 for particles at 15 and 25 micrometer size, respectively.

CMP-PCT in view of Terlevich teaches this limitation.

Specifically, CMP-PCT teaches that its solutions contain no particles visible after extended periods of storage in plastic vials at either 4-8ºC or 25ºC and 60% relative humidity:

- "the composition has no visible particles after storage at 4-8°C for 3-months [to] 96-months." (Ex-1007 at 3:13-17.)
- "the composition has no visible particles after storage at about 25°C and 60% relative humidity for 3-months [to] 24-months, or longer." (*Id.* at 3:18-21.)

CMP-PCT also teaches the use of standardized tests to evaluate the presence of particles (Ex-1007 at 11:30-32) and preparing RTU solutions based on the teachings of CMP-PCT, Terlevich and Perks would not have been expected to alter the CMP-PCT solution particle content. (Ex-1003-Amiji at ¶¶190-92; §X.A, *supra*.)

Specifically, a POSITA 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. Indeed, Terlevich's RTU containers had already been used commercially for at least 13 years, i.e., were a known, conventional RTU container option and stably maintained RTU potassium phosphate solutions. (Ex-1003-Amiji at ¶193; Ex-1009, Ex-1026.) Further, Terlevich's plastic containers did not contain leachable aluminum, and containers like Terlevich's were well-known to prevent moisture and oxygen penetration, thereby preventing solution degradation and particulate generation. (Ex-1003-Amiji at ¶¶194-95; Ex-1013 at 317 (discussing LVP "semi-

rigid plastic containers" and "the sterile formulation of LVP necessitates the use of containers with good barrier properties.".)

Based on the foregoing, a POSITA would have reasonably expected the RTU solutions taught by CMP-PCT, Terlevich, and Perks, when stored in a suitable RTU container, such as the "semi-rigid cylindrical polyethylene container" of Terlevich, to achieve "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 25 micrometer size, respectively." Further, autoclaving of parenteral packaging was conventional. (Ex-1003-Amiji at ¶196; Ex-1033 at 1:17-26 and Ex-1035 at 7:10-15 (explaining steam sterilization (autoclaving) is industry standard); Ex-1007 at 5:25-6:4, 18:24-27 (autoclaving taught by CMP-PCT).)

Thus, claim 6 is obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶197.)

[Claim 7] The solution of claim 1, wherein the solution has…a change in phosphorus of no more than 1% absolute.
[Claim 8] The solution of claim 1, wherein the solution has…a change in potassium of no more than 2% absolute.

CMP-PCT teaches these limitations.

As explained above relative to claim 6, a POSITA would have expected solution stability using appropriate pharmaceutical grade RTU containers, such as the Terlevich container. Further, CMP-PCT teaches its solutions "were assayed *over*

time for appearance, visual particulate matter, *potassium, KMP, and KDP*, according to the respective LISP assays," and "*none* of the vials demonstrated any visible particulate matter at the time of manufacture and after storage for 18-months at 4-8°C, 25°C/60% RH, and 40°C/75% RH." (Ex-1007 at 18:24-34.) These disclosures inform a POSITA that the solutions of CMP-PCT are stable. Indeed, because (a) the CMP-PCT "vials were assayed over time for …potassium, KMP, and KDP," and (b) CMP-PCT does not disclose any issues with any of "potassium, KMP, and KDP," a POSITA would have reasonably expected the phosphorous and potassium concentrations to be stable after many months of storage in a conventional RTU container. (Ex-1003-Amiji at ¶¶198-200.)

Perks (Ex-1030) confirms the solutions would be stable. Even though Perks used a non-RTU container (standard PVC IV bags[9]), Perks' phosphates solutions were substantially stable over a period of 63 days. Using conventional RTU containers would make such solutions highly stable because RTU containers prevent water loss, which was the reason the Perks solution concentrations changed. (Ex-1030 at 7 (Objective), 10-11 (Tables 1-2 showing solution stability for 63 days), 9

[9] A POSITA knew that a standard PVC bag was not a suitable RTU container; *see* IX.A.4; Ex-1030.

and 12 (attributing minor concentration change to "water loss from the PVC bags.").)

Indeed, Perks concluded:

> "When measurements were corrected for water loss, *the concentrations of both sodium and phosphate* ***remained unchanged***…" (*Id.* at 12.)

Accordingly, a POSITA would have reasonably expected diluted CMP-PCT solutions stored in an appropriate RTU container to achieve the requirements of claims 7-8, i.e., "a change in phosphorus of no more than 1% absolute" and "a change in potassium of no more than 2% absolute." (Ex-1003-Amiji at ¶¶201-02.)

Thus, claims 7 and 8 are obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶203.)

[Claim 9] The solution of claim 1, wherein the solution is packaged in a flexible polyolefin container, optionally at a volume of 100 mL.

Claim 9 requires a "flexible polyolefin container." The volume requirement of 100 ml is optional. Terlevich teaches claim 9.

Terlevich teaches that its RTU solutions are stored in a "*semi-rigid* cylindrical polyethylene container." (Ex-1009 at 1326.) A POSITA knew that *semi-rigid* polyethylene containers are "flexible polyolefin containers" because (a) they are made of polyethylene, which is a polyolefin and was known to be flexible, and (b) are "semi-rigid," i.e., have some flexibility, otherwise the author would have not used the word "semi-" with the word "rigid." (Ex-1003-Amiji at ¶¶204-05; Ex-1013

at 308 ("Both HDPE and LDPE…have been used for both SVP and LVP products," i.e., flexible containers.); Ex-1034 at 6:54-64 (explaining polyolefins include polyethylene).) Further, as explained above relative to claims 6-8, it was obvious to use the "semi-rigid polyethylene containers" of Terlevich to package the RTU solutions taught by the combination of CMP-PCT, Terlevich and Perks. (Ex-1003-Amiji at ¶206.)

Thus, Terlevich teaches this limitation, and claims 9 is obvious over the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa. (Ex-1003-Amiji at ¶207.)

[Claim 11, 11.0] A sterile ready-to-use premixed pharmaceutical product stored in a flexible polymeric container,

CMP-PCT in view of Terlevich teaches a "sterile ready-to-use premixed pharmaceutical product" for the reasons provided above relative to claim 1, limitation 1.0.

Terlevich teaches "a flexible polymeric container" for the same reasons provided above relative to claim 9. As explained above relative to claims 6-8, a POSITA would have found it obvious to use the "semi-rigid polyethylene containers" of Terlevich to package the RTU solutions taught by CMP-PCT, Terlevich and Perks.

Thus, CMP-PCT in view of Terlevich teaches this limitation. (Ex-1003-Amiji at ¶¶208-11.)

[11.1] wherein the pharmaceutical product comprises a potassium phosphates in an aqueous sodium chloride solution containing (a) less than 50 mcg/L aluminum,

The CMP Art in view of Terlevich, optionally in view of Ogawa, teaches this limitation for the same reasons provided above relative to limitations 1.0 and 1.2. (Ex-1003-Amiji at ¶212.)

[11.2] (b) about 15 mmol/100 ml phosphorus, and,

CMP-PCT in view of Terlevich and Perks teaches this limitation for the reasons provided above relative to limitation 1.1. (Ex-1003-Amiji at ¶213.)

[11.3] (c) about 22 mEq/100 mL potassium.

CMP-PCT in view of Terlevich and Perks teaches this limitation for the reasons provided above relative to claim 3. (Ex-1003-Amiji at ¶214.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, teaches all limitations of, and renders obvious, claim 11. (Ex-1003-Amiji at ¶215.)

[Claim 17, 17.0] A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising:
[17.1.A] administering, without prior dilution, an isotonic, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container

The CMP Art in view of Terlevich teaches these limitations.

CMP-PCT teaches to intravenously administer its inventive compositions to patients in need of phosphorus replacement therapy. (Ex-1007 at 4:23-5:9.) Further, as shown in claim 1, limitation 1.0, the CMP Art in view of Terlevich disclose

isotonic, sterile, ready-to-use solutions comprising potassium phosphates and sodium chloride solution. Such solutions would ***not*** be diluted prior to administration because they are RTU, as taught by Terlevich. (Ex-1003-Amiji at ¶¶216-18.)

Also, as explained above relative to claim 11, limitation 11.0, Terlevich teaches the use of "semi-rigid cylindrical polyethylene container[s]," which reads on the "flexible container" requirements of the claims. (Ex-1003-Amiji at ¶219.)

Thus, the CMP Art in view of Terlevich teaches this limitation. (Ex-1003-Amiji at ¶220.)

[17.1.B] 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;

CMP-FDA teaches this limitation. Specifically, §2.3, Table 2 of CMP-FDA entitled "Recommended Daily Dosage of POTASSIUM PHOSPHATES INJECTION for Parenteral Nutrition" teaches how much diluted CMP solution should be administered on a daily basis to patients of various ages, and 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-1003-Amiji at ¶¶221-222; Ex-1008 at 4; Ex-1027 at 6.)

Thus, CMP-FDA teaches this limitation. (Ex-1003-Amiji at ¶223.)

[17.2] wherein the solution comprises about 15 mmol/100 ml phosphorus,

CMP-PCT in view of Terlevich and Perks teaches this limitation for the reasons provided above relative to limitation 1.1. (Ex-1003-Amiji at ¶224.)

[17.3] about 22 mEq/100 mL potassium, and

CMP-PCT in view of Terlevich and Perks teaches this limitation for the reasons provided above relative to claim 3. (Ex-1003-Amiji at ¶225.)

[17.4] less than 50 mcg/L aluminum.

CMP-PCT, optionally in view of Ogawa, teaches this limitation for the reasons provided above relative to limitation 1.2. (Ex-1003-Amiji at ¶226.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, teaches all limitations of and renders obvious claim 17. (Ex-1003-Amiji at ¶227.)

[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.

Claim 18 only requires one of the above rates of infusion to be achieved because it states "*or*" between the two different infusion rates.

CMP-FDA teaches claim 18. Specifically, for peripheral central venous administration, CMP-FDA teaches:

> "The maximum recommended infusion rate is approximately phosphorus 15 mmol/hour." (Ex-1008 at 3; Ex-1027 at 5.)

(Ex-1003-Amiji at ¶¶228-29.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, renders obvious claim 18. (Ex-1003-Amiji at ¶230.)

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

CMP-FDA teaches this limitation:

> "The final parenteral nutrition solution is for intravenous infusion into a peripheral or central vein." (Ex-1008 at 4; Ex-1027 at 6.)[10]

(Ex-1003-Amiji at ¶231.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, renders obvious claim 19. (Ex-1003-Amiji at ¶232.)

[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.

CMP-PCT in view of Terlevich teaches this limitation.

Specifically, as explained above relative to claims 6-8, it was obvious to use the "semi-rigid polyethylene containers" of Terlevich to package RTU solutions, and a POSITA would have expected the RTU solutions taught by CMP-PCT, Terlevich and Perks to remain stable when stored for 3-months or more in a suitable pharmaceutical grade RTU container, such as Terlevich's RTU container, as confirmed by Perks. Further, CMP-PCT teaches that its solutions can be administered even after 24-months of storage at 25ºC and 60% relative humidity

[10] The AAPA also admits this limitation was known.

(RH). (Ex-1007 at 3:18-21, 4:23-5:9.) 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 25ºC and 40% RH because (a) the CMP-PCT solutions are already proven stable after *24-months* of storage at 25ºC and 60% RH, and (b) with the appropriate, conventional RTU container, such as the Terlevich container, the lower relative humidity would not meaningfully change the outcome because, as explained above relative to claims 6-8, such containers generally prevent unwanted permeation of water or oxygen. (Ex-1003-Amiji at ¶¶233-35.)

Thus, the CMP Art in view of Terlevich and Perks, optionally in view of Ogawa, renders obvious claim 20. (Ex-1003-Amiji at ¶236.)

XI. Ground 2: Claims 9-11, 14-15, and 17-20 are obvious in view of the Ground 1 Art and Nevakar

A. Scope, Content and Motivation to Combine

Various Challenged Claims of the '291 patent require (a) the use of flexible polymer (e.g., polyolefin) containers with RTU solutions (claims 9-11, 14-15, 17-20), (b) a container volume of 100 ml (claims 9, 14), or (c) the use of a secondary metallized overwrap (claims 10, 15). However, as explained in §IX.A.4, the '291 patent does not purport to have invented new RTU containers, nor could it because (a) ready-to-use, flexible, multiple layer plastic containers for parenteral

administration were already well known, and (b) the '291 patent simply used off-the-shelf containers to store its solutions. (Ex-1003-Amiji at ¶¶237-39.)

As explained in Ground 1, CMP-PCT teaches the use of glass or plastic vials while Terlevich teaches the use of semi-rigid polymeric containers, but neither reference teaches the use of a 100 ml flexible container for use with ready-to-use solutions or the use of a secondary metallized overwrap. Nonetheless, such containers and secondary metallized overwraps were well known. (*Id.* at 239.)

As one example, Nevakar (Ex-1011)[11] teaches flexible polymeric containers suited for use with ready-to-use solutions, which containers may include a secondary metallized overwrap:

> "***[A] polymeric container*** that includes the antioxidant-free and ***storage stable ready-to-administer composition***…wherein the container is a blow-fill-seal (BFS) container or ***flexible IV bag***. For example, ***suitable polymeric containers may have a volume of between 100 mL and 1,000 mL***, and ***may be further enclosed in a metallized over-container***." (Ex-1011 at 0015.)
>
> "*For example, the polymeric container may be configured as a flexible bag with a volume of at least 100 ml* [and]…may be manufactured from [various polymers]. *Such polymeric containers*

[11] RTU parenteral containers have been known for decades; Nevakar is just one example. (§IX.A.4, *supra*; Ex-1003-Amiji at ¶¶56-58, 121; Exs. 1031-37.)

> *may preferably, but not necessarily have a reduced oxygen permeability (e.g., where no overwrap is used).* … Other additional properties include reduced oxygen permeability that can be achieved in a variety of manners, *including multi-layered polymer and/or metal films* that may also include oxygen scavenging materials." (*Id.* at 0037.)

A POSITA would have been motivated to use the polymeric containers and secondary metallized overwrap described by Nevakar with the ready-to-use solutions taught by the Ground 1 art (the CMP Art, Terlevich, Perks (Exs. 1007-09, 1027, 1030)). Nevakar describes that its containers are well-suited for use with ready-to-use solutions and assists in maintaining the stability of such solutions, which is an important feature of CMP-PCT. (Ex-1007 at 3:13-4:15; Ex-1011 at 0015, 0024, 0035-37.) Further, because Nevakar's containers are multilayered and use moisture impermeable polymers, a POSITA would have found Nevakar's containers well-suited for storing parenteral solutions for extended periods of time, as expressly desired by CMP-PCT. (Ex-1003-Amiji at ¶¶240-41.)

A POSITA would also have had reasonable expectation of using Nevakar's containers with the ready-to-use solutions taught by the Ground 1 art because it would have been simple to package the ready-to-use solutions of the Ground 1 art using the Nevakar containers. (Ex-1011 at 0035-36 (showing simplicity of filling RTU containers with solution); *see also* Ex-1032 (showing conventional manner of

filling RTU containers with solution).) A POSITA also would have reasonably expected the ready-to-use solutions taught by the Ground 1 art to be storage stable for extended periods of time because Nevakar discloses its containers are suited for that purpose, and Nevakar discloses multilayered plastic materials and secondary metallized overwraps known to prevent evaporation and oxygen penetration. (Ex-1003-Amiji at ¶242; Ex-1011 at 0015, 0037; Ex-1013 at 309, 317-18; Ex-1033 at 1:26-2:5.)

Accordingly, a POSITA would have found it obvious to use the Nevakar containers with the ready-to-use solutions taught by the Ground 1 art. (Ex-1003-Amiji at ¶243.)

B. The Ground 1 art plus Nevakar render obvious claims 9-11, 14-15, and 17-20

[Claim 9] The solution of claim 1, wherein the solution is packaged in a flexible polyolefin container, optionally at a volume of 100 mL.

As explained above in §XI.A, it was obvious to combine the teachings of Nevakar with the Ground 1 art. Although claim 9 includes one mandatory feature and one optional features (volume), Nevakar teaches all claimed features.

Specifically, Nevakar disclose the use of 100-1000 ml flexible polyolefin bags for use with ready-to-use solutions:

> "***[A] polymeric container*** that includes the antioxidant-free and ***storage stable ready-to-administer composition***…wherein the container is a blow-fill-seal (BFS) container or ***flexible IV bag***. For

> example, ***suitable polymeric containers may have a volume of between 100 mL and 1,000 mL***, and may be further enclosed in a metallized over-container." (Ex-1011 at 0015.)
>
> "For example, *the **polymeric** container may be configured as a **flexible bag** ...*wherein the polymeric bag may be manufactured from polyvinyl chloride, ***polyethylene, polypropylene***…. Other additional properties include *reduced oxygen permeability* that can be achieved in a variety of manners, *including **multi-layered** polymer and/or metal films* that may also include oxygen scavenging materials." (*Id.* at 0037.)

(Ex-1003-Amiji at ¶¶244-46.) A POSITA would recognize that many of the polymers described by Nevakar, including polypropylene and polyethylene, are flexible polyolefins. (Ex-1003-Amiji at ¶247; Ex-1034 at 6:54-64.)

Thus, the Ground 1 art in view of Nevakar teaches and renders obvious claim 9. (Ex-1003-Amiji at ¶248.)

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

Nevakar teaches this limitation.

Specifically, Nevakar disclose that its flexible bags may be contained in a secondary metallized (aluminum) overwrap:

> "[S]uitable polymeric containers may have a volume of between 100 mL and 1,000 mL, and ***may be further enclosed in a metallized over-container***." (Ex-1011 at 0015.)

> "[A] **suitable overwrap** may comprise a polypropylene base layer that is coupled to a **thin aluminum layer** (e.g., thickness between 10 and 50 micrometer), which may be covered by an oriented polyester layer (e.g., commercially available as MEDIFLEX AUAT™ from Amcor Flexibles, Gent, Belgium)." (*Id.* at 0037.)

Doing so further protects the solution from premature degradation. ((Ex-1003-Amiji at ¶¶249-51; Ex-1033 at 1:26-2:5.) Thus, the Ground 1 art in view of Nevakar teaches and renders obvious claim 10. (Ex-1003-Amiji at ¶252.)

[Claim 11, 11.0] A sterile ready-to-use premixed pharmaceutical product stored in a flexible polymeric container,

For the reasons provided above relative to Ground 1, limitation 11.0, CMP-PCT in view of Terlevich teaches a "sterile ready-to-use premixed pharmaceutical product." For the reasons provided above relative to claim 9, Nevakar teaches "a flexible polymeric [polyolefin] container." Further, as explained above relative to §XI.A, a POSITA would have been motivated to apply Nevakar's flexible polymeric container teachings with the Ground 1 art, and with a reasonable expectation of success. Thus, the Ground 1 art in view of Nevakar teaches this limitation. (Ex-1003-Amiji at ¶¶253-56.)

[Claim 11, 11.1-11.3]

The Ground 1 art teaches limitations 11.1.-11.3 for the same reasons provided above in Ground 1, limitations 11.1-11.3.

Thus, the Ground 1 art in view of Nevakar teaches all limitations of and renders obvious claim 11. (Ex-1003-Amiji at ¶¶257-60.)

[Claims 14-15] The pharmaceutical product of….

Nevakar teaches the limitations of claims 14-15 for the same reasons provide above relative to claims 9-10, respectively. Thus, the Ground 1 art in view of Nevakar teaches all limitations of, and renders obvious, claims 14-15. (Ex-1003-Amiji at ¶¶261-63.)

[Claim 17, 17.0] A method of…

The Ground 1 art teaches this limitation for the reasons provided in Ground 2, claim 17, limitation 17.0. (Ex-1003-Amiji at ¶264.)

[17.1.A] administering…

The Ground 1 art teaches "administering, without prior dilution, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution" for the reasons provided in Ground 2, claim 17, limitation 17.1.

Nevakar teaches flexible containers suited for use with the RTU solutions of Ground 1 for the reasons described above in §XI.A and claim 9, and a POSITA would have been motivated to apply Nevakar's flexible polymeric container teachings with the Ground 1 art, and with a reasonable expectation of success as explained in §XI.A.

Thus, the Ground 1 art in view of Nevakar teaches this limitation. (Ex-1003-Amiji at ¶¶265-67.)

[17.1.B]-[17.4]

The Ground 1 art teaches limitations 17.1.B-17.4 for the same reasons provided above in Ground 1, limitations 17.1.B-17.4.

Thus, the Ground 1 art in of Nevakar teaches all limitations of and renders obvious claim 17. (Ex-1003-Amiji at ¶¶268-72.)

[Claim 18-19]

The Ground 1 art teaches claims 18-19 for the same reasons provided in Ground 1, claims 18-19. Thus, the Ground 1 art in view of Nevakar renders obvious claims 18-19. (Ex-1003-Amiji at ¶¶273-76.)

[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.

As explained in Ground 1, CMP-PCT teaches that its solutions can be administered even after 24-months of storage at 25ºC and 60% relative humidity (RH) in plastic vials. (Ex-1007 at 3:18-23, 4:23-5:9.) A POSITA would have reasonably expected to achieve this limitation when using the flexible polymeric containers of Nevakar to store the RTU potassium phosphate solutions taught by the Ground 1 art because, as explained above in relative to claim 9, Nevakar discloses multilayered containers that use moisture impermeable polymers known to prevent evaporation and oxygen penetration and Perks confirms solution stability without evaporation. Accordingly, a POSITA would have expected the RTU potassium phosphate solutions taught by the Ground 1 art to be stable for successful

administration "after storage of at least 3 months at 25° C and 40% relative humidity" when stored in the Nevakar containers. (Ex-1003-Amiji at ¶¶277-79.)

XII. Conclusion

For the foregoing reasons, Petitioner respectfully requests cancellation of claims 1, 3-11, 14-15, and 17-20.

Respectfully submitted,
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Date: April 11, 2025

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CERTIFICATE OF SERVICE

The undersigned certifies that a true and correct copy of the Petition together with all exhibits identified in the above Table of Exhibits and Petitioner's Powers of Attorney, have been served on the Patentee via Priority Mail Express or by means at least as fast and reliable as Priority Mail Express on the below date, at the following address:

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