

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

U.S. Patent No. 11,925,661

**DECLARATION OF DR. MANSOOR M. AMIJI,
UNDER 37 C.F.R. § 1.68 IN SUPPORT OF PETITION FOR
INTER PARTES REVIEW**

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I, Dr. Mansoor M. Amiji, do hereby declare as follows:

I. INTRODUCTION

1. I make this declaration based upon my own personal knowledge and, if called upon to testify, will testify competently to the matters stated herein.

2. I have been asked by Petitioner to provide my expert opinion in connection with the *Inter Partes* Review of U.S. Patent No. 11,925,661 (“the ’661 patent”) to Pandya, et al. concerning whether the ’661 patent is unpatentable over certain prior art. This declaration is a statement of my opinions on issues relating to the patentability of claims 1–20 (the “Challenged Claims”) of the ’661 patent. As I explain more fully below, it is my opinion that all of the Challenged Claims would have been anticipated or obvious to a person of ordinary skill in the art (“POSITA”) at the time of the alleged invention.

3. I am being compensated for my work in this matter at my standard hourly rate. I am also being reimbursed for reasonable and customary expenses associated with my work and testimony in this investigation. My compensation is not contingent on the outcome of this matter or the specifics of my testimony.

4. I have reviewed and considered the following documents in connection with my analysis of the ’661 patent:

Exhibit	Description
1001	U.S. Patent No. 11,925,661 (the “’661 patent”)

Exhibit	Description
1002	File history for the '661 patent
1004	File history for U.S. Patent Application No. 17/499,001
1005	File history for U.S. Provisional Patent Application No. 63/090,518 (“’518 provisional”)
1006	U.S. Patent Application Publication No. 2022/0110969 (“Nivagen-1” or “the ’001 application”)
1007	International Patent Application Publication No. WO2020/081118 (“CMP-PCT”)
1008	Federal Drug Administration Drug Label for “POTASSIUM PHOSPHATES injection, for intravenous use,” September 2019 (“CMP-FDA”)
1009	Terlevich, A., et al. “Refeeding syndrome: effective and safe treatment with Phosphates Polyfusor.” <i>Alimentary pharmacology & therapeutics</i> 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. <i>Chemical and Pharmaceutical Bulletin</i> , 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	Sealed Air Product Data Sheet for Nexcel® M312 Film
1013	Nema, S. and Ludwig, J.D. eds., 2010. <i>Pharmaceutical Dosage Forms: Parenteral Medications</i> , Third Edition, Volume 1: Formulation and Packaging, 2010 Informa Healthcare, CRC Press. Chapters 5 and 12 ISBN-13: 9781420086430
1014	Rowe, Raymond C., Paul Sheskey, and Marian Quinn. “Handbook of Pharmaceutical excipients,” pp. 637-40, 656-661 (2009) ISBN: 9781582121352

Exhibit	Description
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
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	Redline comparison of the text of US2022/0110969 and US2023/0405045
1023	Declaration of Mina Ching from the Internet Archive (archive.org)
1024	Declaration of Dr. Sylvia Hall-Ellis, Ph.D.
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
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.

Exhibit	Description
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

5. In forming the opinions expressed below, I have considered:

- a) the documents listed above;
- b) the relevant legal standards, including the standards for anticipation, obviousness, priority, written description, and any additional authoritative documents as cited in the body of this declaration; and
- c) my own knowledge and experience based upon my work in the field of parenteral solutions as described below, as well as the following materials.

6. Unless otherwise noted, all emphasis in any quoted material has been added.

II. QUALIFICATIONS AND PROFESSIONAL EXPERIENCE

7. My complete qualifications and professional experience are described in my *Curriculum Vitae*, a copy of which can be found in Exhibit 1029. The following is a brief summary of my relevant qualifications and professional experience.

8. I am an expert in the field of pharmaceutical sciences and drug formulation development and characterization. Specifically, I specialize in drug formulation development and targeted delivery of therapeutics and have extensive experience with various types of pharmaceutical formulations and delivery systems. I have extensive experience in the development of parenteral solutions, including those administered intravenously and have familiarity with the regulatory requirements for tonicity, sterility, safety, and quality control. I have been an expert in this field since prior to the year 2000. I have relied upon my training, knowledge, and experience in the relevant art to form my opinions.

9. In 1988, I graduated with honors from Northeastern University and received a Bachelor of Science degree in Pharmacy and became a Registered Pharmacist in Massachusetts. In 1992, I received a Ph.D. in Pharmaceutical Science/Pharmaceutics from the School of Pharmacy and Pharmaceutical Sciences at Purdue University, under the supervision of Showalter Distinguished Professor Kinam Park. During my graduate studies at Purdue University, I took several

pharmaceutics courses and had hands-on training in pharmaceutical formulations during my graduate training.

10. My doctoral dissertation entitled “Surface Modification of Biomaterials with Water-Soluble Polymers: A Steric Repulsion Approach” focused on surface modification with water-soluble polymers for steric repulsion of proteins and cells from biomaterials to improve their compatibility in the body. and water-soluble polymers. During this project, I utilized various polymeric materials and surface modification methods to develop biocompatible materials that could resist protein adsorption as well as cell and bacterial adhesion to improve compatibility with blood and other biological fluids.

11. After receiving my Ph.D. in 1992, I worked as a Senior Research Scientist for Columbia Research Laboratories (CRL) in Madison, Wisconsin. At CRL, I worked on polymeric delivery systems for various types of therapeutic agents.

12. I am currently a University Distinguished Professor and Professor of Pharmaceutical Sciences in the School of Pharmacy, Bouve College of Health Sciences at Northeastern University in Boston, Massachusetts. I am also jointly appointed as a Professor of Chemical Engineering in the College of Engineering at Northeastern University. I am also currently an Affiliate Faculty Member in the Department of Biomedical Engineering at Northeastern University. I have taught

and carried out research in pharmaceutical sciences at Northeastern University since 1993, and from 2010 to 2016, I served as the Chairman of the Department of Pharmaceutical Sciences. In 2000, I was a Visiting Research Scholar in the Department of Chemical Engineering at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts, in the laboratory of Professor Robert Langer.

13. As a tenured faculty member at Northeastern University, I have 32 years of experience in teaching physical pharmacy and drug formulations to both graduate and undergraduate students. In theory and laboratory courses that I have taught and continue to teach, I extensively cover the manufacturing, composition, physico-chemical properties, and pharmacokinetics of pharmaceutical formulations and delivery systems. I also serve as a consultant to several pharmaceutical, biotechnology, and medical device companies regarding product development and drug delivery.

14. I have published extensively over the course of my career and am ranked as a Thompson-Reuters Highly Cited (top 1%) author in Pharmacology and Toxicology. I have edited and coauthored over 10 books, 70 book chapters and more than 400 peer-reviewed scientific articles. The topics of these materials include the design and development of pharmaceutical dosage forms including parenteral aqueous solutions, role of ionic equilibria and buffers in pharmaceutical formulations and quality assessment for safety and efficacy, pharmacokinetics, and

the use/formulation of related excipients and methods. I have been involved in and consulted on multiple projects over the years, both in industry and academia, about the aforementioned topics. To that end, I have also taught courses in physical pharmacy, pharmaceutics; drug design, evaluation, and development; dosage forms; and pharmacokinetics.

15. In 2002, I co-edited a teaching textbook “Applied Physical Pharmacy – 1st Edition”, published by McGraw-Hill to specifically cover topics such as pH, buffers and isotonic solutions, colligative properties, solubility, and dispersions. This book is now in its 3rd edition and is used extensively to teaching these concepts to pharmacy students in the United States and throughout the world.

16. I have served as a grant reviewer for the National Institutes of Health, the Department of Defense, the United States Department of Agriculture, and the American Chemical Society. I am a member of several professional and industrial societies, including the American Association of Pharmaceutical Sciences (AAPS) and the Controlled Release Society (CRS), and have participated as a reviewer for more than 80 scientific journals.

17. I have also received a number of professional awards and honors, including the Nano Science and Technology Institute (NSTI) Fellowship Award for Outstanding Contributions towards the Advancement in Nanotechnology, Microtechnology, and Biotechnology in 2006; a Fellowship and Meritorious

Manuscript Award from the AAPS in 2007; the Tsuneji Nagai Award from the CRS in 2012; the Northeastern University School of Pharmacy Distinguished Alumni Award in 2016; and Purdue University College of Pharmacy Distinguished Alumni Award in 2019. Over the course of my career, I have advised numerous post-doctoral associates, doctoral students, master's students, visiting scientists, and research fellows.

18. I am also the inventor or co-inventor on a number of issued patents and pending patent applications, including nine issued within the United States.

19. I lecture extensively on various topics on the leading edge of modern pharmaceutical sciences, and I regularly attend numerous worldwide pharmaceutical conferences. I have submitted a large number of abstracts to conferences and journals in the field of pharmaceutical sciences. I have been an invited speaker at national and international scientific conferences.

20. I am a founder of and scientific advisor to many pharmaceutical companies, including Nemucore Medical Innovations, and Targagenix, (now called Recurv Pharma), and Perosomer Therapeutics, which have licensed my patents on different types of drug delivery technologies and are in the process of developing a commercial product.

21. In addition to serving as a long-term member of the AAPS and on the Scientific Advisory Board of the CRS, I have also served as a permanent member of

the National Institutes of Health's grant review panel and many other public funding agencies in the U.S. and across the world. I am an Editor for the Americas of the journal Drug Delivery and Translational Research, an official journal of the CRS, and Associate Editor of several peer-reviewed journals and on the editorial board of about a half dozen other scientific journals.

22. Specifically for this matter, I have broad expertise in parenteral formulations, including those made with electrolytes in aqueous solution, tonicity adjustments, sterility and freedom from pyrogens, and safety of injectable pharmaceutical formulations including the role of contaminants, regulatory requirements, and therapeutic applications.

23. Based on my education, training, and experience, including my research expertise in pharmaceutical product development and drug formulation development of over 32 years, including in the October 2020 or September 2023 time frame, I believe that I am qualified to provide useful technical information regarding the subject matter of this case (parenteral solutions for intravenous administration).

III. LEVEL OF ORDINARY SKILL IN THE ART

24. I understand there are multiple factors relevant to determining the level of ordinary skill in the pertinent art, including (1) the levels of education and experience of persons working in the field at the time of the invention; (2) the

sophistication of the technology; (3) the types of problems encountered in the field; and (4) the prior art solutions to those problems.

25. I understand that the '661 patent was filed on September 5, 2023 and purports to claim priority as a:

“[c]ontinuation-in-part of application No. 17/499,001, filed on Oct. 12, 2021, now U.S. Patent No. 11,813,291.

The '661 patent also purports to claim priority to:

“[p]rovisional application No. 63/090,518, filed on Oct. 12, 2020.”

(Ex-1001, (63), (60) [pages 1].)

26. Note that I may refer to the patent documents identified above as follows: application no. 17/499,001 as “the '001 application,” and provisional application no. 63/090,518 as “the '518 provisional.” Further note that, in referring to the '001 application, I generally refer to the published version of that application, which is U.S. Patent Application Publication No. 2022/0110969 (Ex-1006).

27. I also note that a Person of Ordinary Skill in the Art (POSITA) would have understood that the '661 patent is not entitled to claim priority to the '001 application or the '518 provisional as explained herein.

28. My analysis reflects the views of a person of ordinary skill in the art (“POSITA”) in the field of the '661 patent. A POSITA would have had an advanced degree in chemistry, biology and/or pharmaceuticals, plus a few years (e.g., 2-3) of experience in preparing parenteral formulations. Additional education may serve as

a substitute for a lack of experience and vice versa.

29. I understand there is a dispute about whether the '661 patent is entitled to benefit from the October 12, 2021 filing date of the '001 application and/or the October 12, 2020 filing date of the '518 provisional, or if the '661 patent is only entitled to its actual filing date of September 5, 2023. I note that a POSITA would be defined in the same manner with respect to any of these dates—the difference would be that more prior art would be available and known to a POSITA if the effective filing date of the '661 patent is its actual filing date of September 5, 2023 rather than the earlier October 12, 2021 filing date of the '001 application or the October 12, 2020 filing date of the '518 provisional.

30. For purposes of this Declaration in general and with respect to Ground 1, my statements and opinions, such as those regarding my experience and the understanding of a POSITA generally (and specifically related to the references I consulted herein), are rendered from the perspective of a POSITA as of the September 5, 2023 date. For Grounds 2-3, my statements and opinions are rendered from the perspective of a POSITA as of October 12, 2020, i.e., the earliest possible priority date of the '661 patent. In brief, this is because I understand that Ground 1 relies on a reference that qualifies as prior art if the '661 patent is not entitled to benefit from the filing date of the '001 application or the '518 provisional.

IV. LEGAL STANDARDS FOR ANTICIPATION AND OBVIOUSNESS

31. I am not an attorney. In preparing and expressing my opinions and considering the subject matter of the '661 patent, I am relying on certain basic legal principles that counsel have explained to me. These principles are discussed below.

32. I understand that prior art to the '661 patent includes patents and printed publications in the relevant art that predate the proper priority date of the alleged invention recited in the '661 patent.

33. I have been informed by counsel that a claimed invention is anticipated under 35 U.S.C. § 102 if all limitations of the claim are disclosed, expressly or inherently, by a single prior art reference.

34. I have been informed by counsel that a claimed invention is unpatentable under 35 U.S.C. § 103 if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. I have also been informed by counsel that the obviousness analysis takes into account factual inquiries including the level of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and the claimed subject matter.

35. I have been informed by counsel that the Supreme Court has recognized several rationales for combining references or modifying a reference to show

obviousness of claimed subject matter. Some of these rationales include the following: (a) combining prior art elements according to known methods to yield predictable results; (b) simple substitution of one known element for another to obtain predictable results; (c) use of a known technique to improve a similar device (method, or product) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (e) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and (f) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

36. I have been informed by counsel that, for an obviousness combination relying on multiple teachings, that there should have been a reason or motivation that would have led a person of ordinary skill in the art to combine or modify the relevant teachings in the prior art, and that there should have been a reasonable expectation of success in combining those teachings. I understand from counsel that a motivation to combine may be provided by, for instance, from the prior art teachings themselves and/or knowledge of a person of ordinary skill in the art (POSITA). I further understand from counsel that a reasonable expectation of success relates to the requirements of the claims, and a reasonable expectation of success does not require absolute predictability.

37. I further understand that certain factors may support or rebut the obviousness of a claim. I understand that such secondary considerations include, among other things, commercial success of the patented invention, skepticism of those having ordinary skill in the art at the time of invention, unexpected results of the invention, any long-felt but unsolved need in the art that was satisfied by the alleged invention, the failure of others to make the alleged invention, praise of the alleged invention by those having ordinary skill in the art, and copying of the alleged invention by others in the field. I understand that there must be a nexus—a connection—between any such secondary considerations and the alleged invention. I also understand that contemporaneous and independent invention by others is a secondary consideration tending to show obviousness.

38. I am not aware of any allegations by the named inventors of the '661 patent or any assignee of the '661 patent that any secondary considerations are relevant to the obviousness analysis of any Challenged Claim of the '661 patent.

V. SUMMARY OF THE '661 PATENT

A. General background regarding the claims and specification

39. The '661 patent has twenty claims, all of which are challenged. Claims 1, 11, and 17 are independent claims.

40. The '661 patent relates generally to “[r]eady-to-use (RTU) potassium phosphates solutions for phosphorus replacement therapy are presented that include

potassium phosphate and sodium chloride at a fixed volume with 1.5 to 15 mmol/100 mL phosphorus, no more than 22 mEq/100 mL potassium and less than 50 mcg/L aluminum.” (Ex-1001 at Abstract.)

41. As shown herein, such RTU solutions were already known.

B. The prosecution history of the '661 patent and the '001 application

42. I have reviewed the prosecution history of the '661 patent. From my review, I understand that the U.S. Patent Office Examiner did not issue any rejections against the claims. Instead, the Examiner cited a single reference, U.S. Patent No. 11,141,430 to Koneru, and apparently allowed the claims of the '661 patent because Koneru disclosed a total phosphorous concentration of 1 mM/mL. (Ex-1002 at 22-27, 32-40.)

43. I have also reviewed the prosecution history of the '001 application. I again understand that the U.S. Patent Office Examiner did not issue any rejections against the claims. Instead, the Examiner again cited the same prior art reference (US11141430 to Koneru), and apparently allowed the claims of the '001 application because Koneru disclosed a total phosphorous concentration of 1 mM/mL. (Ex-1004 at 146-153.)

VI. TECHNOLOGY BACKGROUND

44. Below I provide a brief overview of hypophosphatemia due to refeeding syndrome, manners of addressing the same, including the use of parenteral

potassium phosphate solutions, common tonicity agents, and aluminum issues in parenteral solutions, all of which would have been well-known to a POSTIA prior to the '661 patent. I also provide a brief discussion of the prior art references I discuss in the Grounds.

A. Hypophosphotemia Treatment By Intravenous Potassium Phosphate Administration Was Well-Known As Were Ready-To-Use Solutions

45. Hypophosphatemia and manners of treating it were well-known prior to the '661 patent. For instance, in 2003 Terlevich et al. explained:

“Severe hypophosphataemia associated with refeeding syndrome requires treatment with intravenous phosphate to prevent potentially life-threatening complications. However, evidence for replacement regimens is limited and current regimens are complex and replace phosphate inadequately.” (Ex-1009 at 1325.)

Terlevich, thus, endeavored to show an adequate manner of addressing severe hypophosphataemia. Over a 2-year period, Terlevich treated 30 patient with severe hypophosphataemia due to refeeding syndrome, all of which had had a serum phosphate concentration of < 0.50 mmol/L at the diagnosis of refeeding syndrome. (*Id.* at 1326.) All patients were treated with at least one Phosphates Polyfusor (PPF) made by Fresenius Kabi Ltd., Warrington, UK. A PPF “is a [500-ml] sealed semi-rigid cylindrical polyethylene container, with a twist-off seal at one end and a ring tab at the other,” and each “500-mL PPF contains 50 mmol phosphate, 81 mmol

sodium and 9.5 mmol potassium.” (*Id.* at 1325-26.) The PPF treatment by Terlevich was effective:

“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.)

Accordingly, Terlevich recommended:

“[W]hen patients are identified to be at risk of the development of refeeding syndrome, information regarding electrolyte monitoring and treatment, with a regimen which can be easily implemented on general wards, is required. We have shown that, for patients being cared for on general medical and surgical wards, this can be achieved by written advice from a nutrition team, daily blood monitoring for 3 days in at-risk patients and treatment with a PPF containing 50 mmol of phosphate over 24 h.” (*Id.* at 1328.)

46. Many other references disclose the benefit of treatment of hypophosphatemia using parenteral potassium phosphate solutions. For instance, in 2007, Brunelli et al. explained:

“A graded dosing scheme for intravenous phosphate repletion (0.16 mmol/kg over 4 to 6 h, 0.32 mmol/kg over 4 to 6 h, and 0.64 mmol/kg over 8 to 12 h for serum phosphate levels of 0.74 to 0.96, 0.51 to 0.70, and <0.48 mmol/L, respectively) has been efficacious among critically ill, nonobese surgical and trauma patients with normal renal function and normocalcemia. Administration of 0.4 and 0.8 mmol/kg

intravenous phosphate over 30 min to patients with moderate and severe hypophosphatemia, respectively, is also well tolerated.” (Ex-1019 at 2002.)

Brunelli further explained that:

“[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, as compared with historical control subjects who received phosphate repletion via a nonstandardized approach: 76 versus 47%, respectively. The bulk of existing evidence suggests the overall advantage of faster, more aggressive and tailored intravenous phosphate repletion regimens.” (*Id.*)

Table 3, referenced by Brunelli, is reproduced below.

Table 3. Phosphorus repletion protocol^a

Phosphorus Level	Weight 40 to 60 kg	Weight 61 to 80 kg	Weight 81 to 120 kg
<0.32 mmol/L	30 mmol Phos IV	40 mmol Phos IV	50 mmol Phos IV
0.32 to 0.54 mmol/L	20 mmol Phos IV	30 mmol Phos IV	40 mmol Phos IV
0.58 to 0.70 mmol/L	10 mmol Phos IV	15 mmol Phos IV	20 mmol Phos IV

^aReproduced with permission from Taylor *et al.*³⁷ IV, intravenous; Phos, phosphorus. If the patient’s serum potassium is <4.0 mEq/L, then use potassium phosphorus; if the patient’s serum potassium is >4.0 mEq/L, then use sodium phosphorus.

(*Id.*) Thus, since at least 2007, a POSITA knew that intravenous phosphate solutions should be administered according to the weight of the patient and their phosphate serum levels.

47. As another example, in 2016, Wadsworth *et al.* discussed known treatments for severe hypophosphatemia, including use of the PPF described by Terlevich:

“Parenteral phosphate replacement is indicated if the patient has severe hypophosphataemia ($<0.32 \text{ mmol litre}^{-1}$) or is symptomatic....A commonly used treatment is the Phosphate Polyfusor®, a solution containing $50 \text{ mmol PO}_4^{3-}$, 9.5 mmol K^+ , and 81 mmol Na^+ in 500 ml , given over 24 h via a central venous catheter. This preparation should be infused alone, via a dedicated port of a central line, and if given peripherally should have a dedicated cannula. Peripherally, the ideal is to reduce the rate of infusion due to risk of pain and phlebitis at the injection site, but with close monitoring could be given at the same rate as the central dose.” (Ex-1026 at 309.)

Wadsworth also explained that potassium phosphate solutions containing both monobasic potassium phosphate (KMP) and dibasic potassium phosphate (KDP) were known:

“Another common replacement regimen includes that of i.v. potassium phosphates. Products can be a combination of monobasic potassium phosphate and dibasic potassium phosphate. They must be diluted before use in either 0.9% sodium chloride or 5% glucose to a minimum volume of 100 ml , and given at a rate of no greater than 20 mmol of phosphate per hour preferably via a central line. This avoids administrations of high-sodium content fluid, and in patients requiring potassium replacement and phosphate, can be very useful. Dose should

be titrated against plasma phosphate and potassium levels regularly to avoid hyperphosphataemia and hyperkalaemia.” (*Id.*)¹

48. In 2019, CMP DEV LLP a.k.a. CMP Pharma received FDA approval for its potassium phosphate solution having 175 mg KMP and 300 mg KDP per ml. (Exs. 1008, 1017-18, 1027.) The FDA Drug Label associated with this product recommends maximum potassium infusion rates of 6.4 mmol/hour (potassium 10 mEq/hour) for peripheral venous administration and 15 mmol/hour (potassium 23.5 mEq/hour) for central venous administration. (Ex-1008 at 3; Ex-1027 at 5.) The administered phosphorous dosage and rate is dependent on the serum phosphorous concentration and the weight of the patient:

TABLE 1: Recommended Initial or Single Dose of POTASSIUM PHOSPHATES INJECTION in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients 12 Years of Age and Older

Serum Phosphorus Concentration ^a	Phosphorus Dosage ^{b, c}	Corresponding Potassium Content
1.8 mg/dL to 2.4 mg/dL	0.16 mmol/kg to 0.31 mmol/kg	0.25 mEq/kg to 0.49 mEq/kg of potassium
1 mg/dL to 1.7 mg/dL	0.32 mmol/kg to 0.43 mmol/kg	0.5 mEq/kg to 0.68 mEq/kg of potassium
Less than 1 mg/dL	0.44 mmol/kg to 0.64 mmol/kg ^c	0.69 mEq/kg to 1 mEq/kg of potassium

^a Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults. Serum phosphorus concentrations may vary depending on the assay used and the laboratory reference range.

^b Weight is in terms of actual body weight. Limited information is available regarding dosing of patients significantly above ideal body weight; consider using an adjusted body weight for these patients.

^c up to a maximum of phosphorus 45 mmol (potassium 71 mEq) as a single dose.

¹ KMP and KDP are well-known terms for monobasic potassium phosphate (KH₂PO₄ or “potassium hydrogen phosphate”) and dibasic potassium phosphate (K₂HPO₄ or “potassium dihydrogen phosphate”), respectively. (Ex-1007 at 1:11-16; 11:18-20.)

(Ex-1008 at 3; Ex-1027 Table 1.)

49. It was also known to administer potassium phosphate solutions in a ready-to-use (RTU) format. For instance, the Phosphate Polyfusor® (PPF) solution by Fresenius “was commonly used” and contained 50 mmol of phosphate and 9.5 mmol of potassium. (Ex-1026 at 309.) The PPF was administered directly from a “a sealed semi-rigid cylindrical polyethylene container, with a twist-off seal at one end and a ring tab at the other,” and infused “via a central venous catheter...alone, via a dedicated port of a central line, and if given peripherally [it] should have a dedicated cannula.” (Ex-1009 at 1326; Ex-1026 at 309.)

50. Thus, prior to the '661 patent, it was well-known to a POSITA that severe hypophosphatemia was regularly treated using central or peripheral intravenous delivery of potassium phosphate solutions, that the amount and rate of administration depended on the patient’s specific situation, including their serum phosphorous concentration and body weight, and that such solutions could be provided/purchased in a ready-to-use format.

B. Parenteral Potassium Phosphate Solutions Should Be Isotonic

51. For many decades, it has been known that many parenteral solutions, such as potassium phosphate parenteral solutions, should be isotonic prior to administration. As the textbook “*Pharmaceutical Dosage Forms: Parenteral Medications*” explains:

“**Tonicity.** 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. Isotonic solutions exert the same osmotic pressure as blood plasma. Solutions may also exert less (hypotonic) or more (hypertonic) osmotic pressure than plasma. Red blood cells (RBCs; erythrocytes) when introduced into hypotonic solution will swell and often burst (hemolysis) because of diffusion of water into the cell. If the cells are placed into hypertonic solutions, they may lose water and shrink (crenation). In isotonic solutions (e.g., 0.9% sodium chloride) the cells maintain their “tone” and the solution is isotonic with human erythrocytes. Isotonicity of formulation is not always feasible as a result of the high concentrations of drug utilized, the low volumes required for some injections, the wide variety of dose regimens and methods of administration, and product stability considerations. Historically, there has been concern over the osmolality or tonicity of IV infusion fluids because of the large amounts of solution administered to hospitalized patients, but in the last few years there has also been interest in the osmolality of other parental dosage forms.”²

52. Two common tonicity agents are sodium chloride and dextrose, with a concentration of 0.9% NaCl (w/v) or 0.9 g/100 ml being ubiquitous:

² Small volume parenteral solutions are typically 100 ml or less; large volume parenteral solutions are typically more than 100 ml. (Ex-1013 at 76, 317.)

“Sodium or potassium chloride and dextrose are commonly added to adjust hypotonic solutions.” (Ex-1013 at 100; *see also id.* at 93, Table 9.)

“In isotonic solutions (e.g., 0.9% sodium chloride) the cells maintain their “tone” and the solution is isotonic with human erythrocytes.” (*Id.* at 100.)

“Sodium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations, where the primary use is to produce isotonic solutions.” (Ex-1014 at 637.)

“Osmolarity A 0.9% w/v [NaCl] aqueous solution is iso-osmotic with serum.” (*Id.* at 638)

“Another common replacement regimen includes that of i.v. potassium phosphates. Products can be a combination of monobasic potassium phosphate and dibasic potassium phosphate. They must be diluted before use in either 0.9% sodium chloride or 5% glucose to a minimum volume of 100 ml....” (Ex-1026 at 309.)

“Phosphate Buffer Preparation All phosphate buffer solutions (16 or 20 mm) were prepared by dissolving dibasic sodium phosphate and monobasic sodium phosphate in water and adjusting the pH to 7 with sodium hydroxide solution (1 N or 0.1 N). All of the buffer solutions contained 0.9% sodium chloride, which served as a tonicity agent. If necessary, polysorbate 80 (0.02%) was added to the solution.” (Ex-1010 at 540.)

“Objective: To evaluate the physical compatibility and chemical stability of 30 and 150 mmol/L solutions of phosphate, prepared from

sodium phosphate injection, in 5% dextrose in water (D5W) and in 0.9% sodium chloride (normal saline [NS]) and stored in polyvinyl chloride (PVC) bags at 23°C or 4°C over 63 days.” (Ex-1030 at 7.)

53. Indeed, the FDA Drug Label associated with the CMP DEV LLC solution (described above and in more detail below) suggests isotonicity and the use of 0.9% NaCl:

“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.)

“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.” (Ex-1008 at 6; Ex-1027 at 8.)

54. Thus, prior to the '661 patent, a POSITA knew that parenteral solutions, such as parenteral potassium phosphate solutions, should be isotonic and the use of 0.9% NaCl, also known as saline, was a conventional way to prepare/administer an isotonic solution.

C. Aluminum Issues Of Parenteral Solutions Were Well Known

55. Aluminum is undesired and should be avoided in parenteral solutions for several reasons. First, aluminum is known to be toxic and the subject of FDA regulations. As the CMP DEV LLP patent application (Ex-1007; “CMP-PCT”)

explains:

“A high aluminum content conflicts with recent recommendations to minimize the amount of aluminum in parenteral products. For instance, Poole (2011) states that certain patient populations having renal insufficiency can experience problems associated with aluminum toxicity. Poole (2011) also states that recorded manifestations of aluminum toxicity include fracturing osteomalacia and reduced bone mineralization, neurological dysfunction and dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis. In an effort to minimize the possibility that a patient having renal insufficiency will be exposed to unacceptable levels of aluminum in parenteral products, the U.S. Food and Drug Administration ("FDA") has promulgated regulations in an effort to minimize the amount of aluminum in parenteral products. See, e.g., FDA Regulations (2000) and Poole (2008).”

56. Second, even very low levels of aluminum were known to cause the precipitation of insoluble precipitate particles in parenteral solutions. For instance, in 2013 Ogawa evaluated phosphate buffer solutions that included from 25-1000 ppb of aluminum. While none of 25 ppb Al solutions presented insoluble precipitate particles, the 50 ppb Al solutions produced particles:

“For the preliminary study, 25-1000 ppb of Al ions, which was prepared from ICP standard solution, was added to the phosphate buffer solution (16 mm, with 0.02% polysorbate 80), and each solution was placed in a CZ plastic vial and then stored at 5°C. 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.” (Ex-1010 at 543-44.)

In his conclusion, Ogawa again emphasized that solutions with as little as 50 ppb Al may give rise to insoluble precipitate particles in phosphate buffer solutions:

“When 50 ppb and higher concentrations of Al ions were added to the phosphate buffer solution, the formation of white particles containing Al, P and O was detected.” (*Id.* at 545.)

57. A POSITA knew that insoluble precipitate particles must be avoided in phosphate buffer solutions as they are dangerous to the patient and render the solution unusable:

“Among the packaging materials that are compatible with injectable drug solutions, glass containers, such as vials or ampoules, have been widely chosen and used. ... However, these [borosilicate] glass containers, even when made from borosilicate glasses, will unavoidably suffer some undesirable events from being in contact with the drug solutions in long term storage. In certain cases, insoluble particle formation occurs in glass containers when drug products are stored in glass containers. The formation of insoluble particles is one of the most critical incidents for pharmaceutical companies, resulting in recalls of their drug products from the market.” (Ex-1010 at 539.)

“For therapeutic use, the precipitations of Al-phosphate complexes are commonly manufactured by mixing phosphate buffer and aluminum

chloride for adjuvants in vaccines. However, the Al-phosphate complex formation in other injectable drugs is unacceptable because these insoluble particles have the ability to harm the patient's veins. In particular, for development of antibody drugs, particles are a concern for biopharmaceutical manufacturers and regulatory officers based on reports that particles in protein drugs may serve as nuclei triggering the aggregation of the protein, increasing the risk of immunogenicity, and that particles may also enhance the immunogenicity of the protein drug by themselves. 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." (*Id.* at 541.)

58. Finally, a POSITA knew that glass vials should be avoided with phosphate buffer solutions as aluminum from the glass was known to leach into the solution, causing the aluminum concentration to increase over time. As CMP-PCT explains:

"The initial aluminum assays for the aseptic glass vials (2.4 ppm) and terminal sterilized glass vials (5.8 ppm) shows that terminal sterilization is a source of aluminum in the composition. Additionally, aluminum continues to leach from the glass into the composition after storage for an extended period. The following table summarizes the aluminum content for terminal sterilized glass vials stored at either 4-8°C or 25°C/60% RH, initially (0M), at 3-months (3M), at 12-months (12M), and at 18-months (18M)." (Ex-1007 at 19:6-12.)

Ogawa also reported aluminum leaching from borosilicate glass compositions:

“Among the packaging materials that are compatible with injectable drug solutions, glass containers, such as vials or ampoules, have been widely chosen and used. For parenteral drug products, borosilicate glasses (Type I) composed principally of silicon dioxide and boric oxides and soda-lime glasses composed of relatively high levels of sodium oxide and calcium oxide are used. Borosilicate glasses in particular are known to have a good chemical durability and are used commonly in the pharmaceutical industry as the primary container. However, these glass containers, even when made from borosilicate glasses, will unavoidably suffer some undesirable events from being in contact with the drug solutions in long-term storage.” (Ex-1010 at 539.)

“Because the rubber closure used in this study was Al-free, the source of Al should be the borosilicate glass vial used as a container for the sample. 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.” (Id. at 541.)

59. Accordingly, a POSITA knew that plastic containers should be used when possible to avoid the aluminum leaching issue, which also has the added benefit of being able to store the potassium phosphate solutions at room temperature:

“Preparing Phosphate Buffer with Aluminum (Al) Ions

The given concentration of Al ions was prepared by diluting an Al standard solution for inductively coupled plasma (ICP) 1000 mg/L (Kanto Chemical) or an aqueous solution of aluminum chloride

hexahydrate (0.895 g/L; 100 ppm as Al) with the buffer solution. To eliminate the amount of Al eluted from a glass vial, these solutions were stored in CZ plastic vials.” (Id. at 540.)

“Since it was confirmed that neither the plastic vials nor the rubber closures elute Al under this study conditions (data not shown), the amount of spiking of Al ion must be a total content of Al in each sample.” (Ex-1010 at 544.)

“Tests conducted in a plastic vial (e.g., with a medical grade cyclic olefin polymer (COP) with or without a SiO₂ coating) on a composition of the first or second embodiment 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 a composition of the first or second embodiment stored in a plastic vial may be stored at room temperature.” (Ex-1007 at 20:1-7.)

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

60. Some claims of the '661 patent relate to flexible multilayer containers. Such containers have been known for decades. Indeed, the '661 patent does not purport to have invented any such containers—off the shelf products were used, such as those produced by the companies TechnoFlex, Grifols, HaemoPharm, and Informed Fluids. (Ex-1001 at 21:11-24:49, Table 20, “Bag Source”).

61. Nonetheless, ready-to-use, flexible, multiple layer plastic containers for parenteral administration were known prior to the '661 patent. For instance, as the

2010 book entitled “*Pharmaceutical Dosage Forms: Parenteral Medications*” explains:

“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 many decades, many different medical-grade, RTU flexible containers have been described in the patent literature and elsewhere. (*See* Exs. 1031-1037.) Thus, prior to the ’661 patent, a POSITA knew it was conventional to store intravenous and other ready-to-use solutions in flexible multilayer containers.

62. A POSITA also knew to avoid PVC for RTU parenteral solution containers because PVC was known to allow water evaporation and have phthalate leaching issues. (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:

“LVP refer to sterile diluents, electrolytes, irrigating fluids, blood derivatives, nutritional preparations and premixed injectable drugs administered in quantities of over 100 mL. LVP are packaged in semi-rigid plastic containers, *flexible minibags* and, to a lesser extent, glass containers....*The sterile formulation of LVP necessitates the use of containers with good barrier properties...*” (Ex-1013 at 317.)

“Minibags are used for administering lower-volume parenteral admixtures, and most premixed IV solutions are packaged in specially designed minibags. IV minibags usually contain 50- or 100-mL volumes of solution and are made of PETG, PP and various polyethylene-based coextrusion. These containers provide a sterile format consisting of a drug mixed with an appropriate diluent solution.” (*Id.* at 317-18.)

“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.” (*Id.* at 309.)

(*See also* Ex-1031 at 2:40-49 and 4:23-36 (explaining to use polyethylene, which has “low permeability to water,” for storing an intravenous solution); Ex-1033 at 3:66-4:1 (use of multiple layers of polymeric materials “impervious to atmospheric gases, moisture and bacteria.”); Ex-1034 at 3:36-47 (flexible containers must provide “barrier against environmental oxygen and water vapor”), 7:26-31 and 8:43-55 (use of polypropylene and/or polyethylene for multilayered container), Ex-1035 at 1:46-2:67 (“preferred” use of polyolefins, such as polypropylene and polyethylene, to produce multilayer medical containers).)

E. Units and Conversions

63. Various units are used in the prior art, the '661 patent, and the claims.

Below I provide a tutorial on these items.

64. Potassium phosphate solutions often the term “mmol/ 100 ml,” which a POSITA knows means millimoles (mmol) per 100 milliliters.

65. Potassium phosphate solutions often use the term “mg/ml,” which a POSITA knows means milligrams per milliliter.

66. Converting between mmol/100 ml and mg/ml is routine and conventional to a POSITA. First, the molecular weight of the compound is determined. For instance, monobasic potassium phosphate (KMP or KH_2PO_4) has a molecular weight of 136.09 g/mol, while dibasic potassium phosphate (KDP or K_2HPO_4) has a molecular weight of 174.18 mg/mol. (Ex-1008 at 8-9; Ex-1027 at 10.) Then, the molecular weight is used to covert moles to grams, or vice versa.

67. CMP-PCT (discussed below) discloses a solution having 175 mg/ml of KMP. (Ex-1007 at 2:29-32.) It is routine to convert this concentration into mmol/100 ml as I show below.

- $175 \text{ mg/ml} * (100/100) = 17,500 \text{ mg/100 ml}$
- $17,500 \text{ mg/ml} * (1 \text{ g/1000 mg}) = 17.5 \text{ g/100 ml}$
- $17.5 \text{ g/100 ml} * (1 \text{ mol/136.09 g}) = 0.12859 \text{ mol/100 ml}$
- $0.12859 \text{ mol/100 ml} * (1000 \text{ mmol/1 mol}) = 128.59 \text{ mmol/100 ml}$

The same conversions can be done for other ingredients of potassium phosphate solutions (e.g., KDP, potassium, NaCl).

68. The term “mcg/L” is also used in the ’661 patent, the claims and the prior art. A POSITA knows this term means micrograms per liter. A POSITA also knows that 1 ppm (parts-per-million) and 1 ppb (parts-per-billion) is equivalent to 1 milligram per liter and 1 microgram per liter, respectively. Since 1 mg is equal to 1,000 mcg, the conversion between ppm and ppb and mcg/L is:

$$1 \text{ ppm} = 1,000 \text{ mcg/L}$$

$$1 \text{ ppb} = 1 \text{ mcg/L}$$

69. It is also relatively straightforward to calculate milliequivalents (mEq) of each element in the salt from mmoles by dividing the mmoles with the atomic weight of the element. For example, 10 mmoles of monobasic potassium phosphate (KH_2PO_4) will have 0.26 mEq of potassium (atomic weight 39.1 g/mole) (i.e., $10/39.1 = 0.26$).

70. Lastly, it was also well known to a POSITA that percent weight by volume, e.g., 0.9% (w/v) sodium chloride (NaCl) or 5% (w/v) dextrose, refers to the amount of the solute in grams per 100 mL of solution.

VII. PRIOR ART OVERVIEW

71. Below I provide a non-limiting overview of the prior art I apply in the invalidity grounds stated herein. This overview is for background purposes and is not to be taken as an exhaustive list of the teachings of the prior art. I include additional details regarding the prior art in the Grounds below.

A. Nivagen-1 (Ex-1006)

72. Nivagen-1 is U.S. Patent App. Pub. No. 2022/0110969, filed as the '001 application, and published April 14, 2022. (Ex-1006, Cover.) I understand Nivagen-1 is prior art only if the '661 patent is not entitled to claim priority to the '001 application.

73. Nivagen-1 is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

74. My analysis of Nivagen-1 is straightforward: Nivagen-1 is the parent to the '661 patent, and includes many of the same disclosures as that of the '661 patent. In my opinion, the disclosures of the '001 application teach each and every limitation of the Challenged Claims.

B. The CMP Art (Exs. 1007, 1008, 1027)

75. For Grounds 2-3, I apply the CMP Art. 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").

1. CMP-PCT

76. "CMP-PCT" is International Publication No. WO2020/081118 to CMP published April 23, 2020. (Ex-1007, Cover.) I understand CMP-PCT is prior art to

the '661 patent irrespective of its earliest possible priority date.

77. CMP-PCT is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

78. CMP-PCT 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 1:7-9.) The sterile compositions include, for example, “(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.” (*Id.* at 2:30-32.)

2. CMP-FDA

79. CMP-FDA (Ex-1008; Ex-1027) is an FDA Drug Label relating to the intravenous potassium phosphate solutions described by CMP PCT. As I explain below, it is my opinion that CMP-FDA was published and made publicly accessible by the FDA in September 2019 (Ex-1008). Nonetheless, as I also explain below, CMP-FDA was also published and made publicly accessible by the Dailymed website (Ex-1027) no later than September 23, 2020. Collectively, I refer to Ex-1008 and Ex-1027 as “CMP-FDA.” It is my understanding that CMP-FDA is prior art to the '661 patent irrespective of its earliest possible priority date.

80. CMP-FDA is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

81. CMP-FDA provides additional details surrounding the administration of the parenteral solutions described by CMP-PCT including an adjustment of tonicity using 0.9% sodium chloride and manners of administering via a peripheral venous or central venous catheter.

3. CMP-PCT and CMP-FDA relate to the same potassium phosphate solutions

82. A POSITA would have known CMP-FDA relates to the same potassium phosphate solution as that of CMP-PCT for many reasons.

83. First, both CMP-PCT and CMP-FDA relate to the same company. The assignee of the CMP-PCT application is "CMP Development LLC" having an address of 8026 US 264A, Farmville, NC 27828. CMP-FDA lists the distributor as "CMP Pharma Inc." having the exact same address, i.e., 8026 US Highway 264A, Farmville, NC 27828." (Ex-1008 at 9; Ex-1027 at 11.)

84. Second, when the FDA approved the CMP solutions for distribution, the Orange Book listed "CMP DEV LLC" as the owner, i.e., the Orange Book and CMP-PCT list the same company:

**(71) Applicant: CMP DEVELOPMENT LLC [US/US]; 8026
U.S. 264A, Farmville, NC 27828 (US).**

(Ex-1007 at 1)

```
>A>    POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC
>A>    SOLUTION; INTRAVENOUS
>A>    POTASSIUM PHOSPHATES
>A>    +!  CMP DEV LLC                                4500MG/15ML (300MG/ML);
                                                    2650MG/15ML (175MG/ML)
```

(Ex-1018 at 21; Ex-1023 at 48.) Exhibit 1018, i.e., the Orange Book, published no later than December 15, 2019. (Ex-1023 at 17-22 (FDA website for accessing “Additions/Deletions for Prescription and OTC Drug Product Lists” as of December 13, 2019, providing access to Ex-1018); Ex-1023 at 27-56 (Orange Book listing from September 19 published as of December 15, 2019).)

85. Third, both CMP-PCT, CMP-FDA, and the Orange Book include the exact same amounts of KMP and KDP, as the below table shows.

CMP-PCT (Ex-1006) “A first embodiment is directed to a sterile composition for injection, comprising: (a) about <u>175 mg/mL potassium monobasic phosphate</u>; (b) about <u>300 mg/mL of potassium dibasic phosphate</u>;...” (Ex-1006 at 2:30-32.)	CMP-FDA (Ex-1008; Ex-1027) “Each mL contains 175 mg of monobasic potassium phosphate and 300 mg of dibasic potassium phosphate.” (Ex-1008 at 9; Ex-1027 at 10.)	Orange Book (Ex-1018) “POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC ... 4500MG/15ML (<u>300MG/ML</u>); 2650MG/15ML (<u>175MG/ML</u>)” (Ex-1018 at 21.)
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86. Fourth, the Orange Book listing for CMP DEV LLC includes its FDA

application number: 212121 and an approval date of September 19, 2019. (Ex-1018 at 21.) When the FDA sent its approval letter to CMP DEV LLC, it included the same application number (212121) and date (September 19, 2019). (Ex-1017 at 1, 6.) The FDA approval letter was sent to 8026 US Highway 264A, Farmville, NC 27828, i.e., the same address listed for CMP Development LLC in CMP-PCT. (*Id.* at 1.)

87. Fifth, the Approval Package from the FDA (Ex-1017) also included reference number 4494533 in the footer. This is the same reference number included in the footer of Exhibit 1008, indicating FDA approval package 212121 also relates to FDA reference number 4494533, i.e., the FDA drug label for the CMP KMP:KDP solutions.

88. For at least the above reasons, a POSITA would have known that CMP-FDA relates to the same potassium phosphate solution as that of CMP-PCT.

4. Publication and Public Accessibility of CMP-FDA

89. It is my opinion that Exhibit 1008 was published and publicly accessible to those skilled in the art no later than September 23, 2019.

90. First, it is known to a POSITA that the FDA keeps a regular and updated listing of all approved drugs, accessible by the website:

<https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases>

91. By accessing this website, a POSITA can access FDA approved drug label by searching:

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>

92. I have accessed the FDA website many times throughout my career to access drug label information, including before October 12, 2020, and often in the manner I describe herein. To access the CMP FDA drug label, I searched the above website for “Potassium Phosphates” and received the below results:

Search Results for "Potassium Phosphates"

Products listed on this page may not be equivalent to one another.

POTASSIUM PHOSPHATES	
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) NDA #212121 SOLUTION;INTRAVENOUS Discontinued CMP DEV LLC
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) NDA #212832 SOLUTION;INTRAVENOUS Prescription FRESENIUS KABI USA
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) ANDA #216274 SOLUTION;INTRAVENOUS Prescription AM REGENT
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) ANDA #216344 SOLUTION;INTRAVENOUS Prescription AMNEAL
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) ANDA #217726 SOLUTION;INTRAVENOUS Prescription SOMERSET THERAPS LLC
•	POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC) ANDA #217892 SOLUTION;INTRAVENOUS Prescription CIPLA
POTASSIUM PHOSPHATES IN 0.9% SODIUM CHLORIDE	

(See Appendix A.) As shown, the “CMP DEV LLC” product is listed first and with NDA (new drug application) number 212121. I then accessed this new drug application by clicking the link associated with CMP, which provided access to the below. (See Appendix A.)

New Drug Application (NDA): 212121

Company: CMP DEV LLC

 EMAIL

Products on NDA 212121 

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/ Route	Marketing Status	TE Code
 POTASSIUM PHOSPHATES	POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC	4.5GM/15ML (300MG/ML); 2.65GM/15ML (175MG/ML)	SOLUTION; INTRAVENOUS	Discontinued	None

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 212121 

Labels for NDA 212121 

93. A POSITA can access the CMP FDA Drug Label by clicking the down arrow for “Labels for NDA 212121,” as shown below.

Labels for NDA 212121 

CSV Excel Print

Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
09/19/2019	ORIG-1	Approval	Label (PDF)	

Showing 1 to 1 of 1 entries

Then, by clicking “Label (PDF),” the CMP Drug Label is provided, which label is identical to that of Ex-1008, and which label states “Revised Sept. 2019.” (See Appendix A.) A POSITA would have expected the CMP-FDA Drug Label to be published no later than September 23, 2019, as the FDA “typically adds information to Drugs@FDA about approved drug and biological products within two business days of approval,” and September 23, 2019, was two business days after September 19, 2019:

9. How often do you update Drugs@FDA?

We update the Drugs@FDA database every day (sometimes several times throughout the day) with new information about approved drug and biological products. We typically add information to Drugs@FDA about approved drug and biological products within two business days of approval. This may include information from original NDAs/BLAs, efficacy supplements, or labeling supplements.

(See Appendix A.)

94. I have accessed FDA drug labels many times in the past, including before 2020, and using the same or a generally similar protocol to that described above. Generally, the FDA drug labels are available to the public as shown above and I would have expected a POSITA interested in accessing the CMP-FDA drug label to have been able to do so no later than September 23, 2019 (within two business days of the drug label approval date). Accordingly, it is my opinion that Exhibit 1008 was likely published and publicly accessible by September 23, 2019.

95. For many of these same reasons, the CMP FDA approval letter (Ex-1017) would have been published and publicly accessible around the same time as

the CMP FDA drug label, i.e., on or around September 23, 2019. A POSITA can access the CMP FDA approval letter from the same website location as the drug label by clicking the down arrow for “Approval Date(s) and History...” of the NDA212121 page as shown below.

Approval Date(s) and History, Letters, Labels, Reviews for NDA 212121						
Original Approvals or Tentative Approvals						
CSV	Excel	Print				
Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	Notes
09/19/2019	ORIG-1	Approval	Type 5 - New Formulation or New Manufacturer	PRIORITY	Label (PDF) Letter (PDF) Review	
Showing 1 to 1 of 1 entries						

Then, by clicking “Letter (PDF),” the CMP approval letter is provided, which label is identical to that of Ex-1017. (See Appendix A.)

96. Irrespective of the above, as the Internet Archive shows, the CMP FDA Drug Label was published and publicly accessible to a POSITA no later than September 23, 2020, via the website:

- <https://dailymed.nlm.nih.gov>

(Ex-1023 at 5-16.) The “Dailymed” website (dailymed.nlm.nih.gov) is commonly

used by persons in the field of the '661 patent for accessing FDA drug labels and other materials approved by the FDA. For convenience, I separately attach the Internet Archive version of the DailyMed website as Exhibit 1027.

97. I have compared the contents of Exhibit 1008 to that of the Dailymed website (Ex-1023, at 5-16 which I include as Ex-1027) and find the content to be generally identical. Both include the same sections (e.g., Highlights of Prescribing Information (front page of Ex-1008; pages 1-2 of Ex-1027) and Full Prescribing Information and §§1-17 thereof (Ex-1008 at 1-9; Ex-1027 at 2-11) and essentially identical text in those sections.

98. Thus, a POSITA would have been able to access the publicly available CMP FDA Drug Label using the Dailymed website no later than September 23, 2020, which is prior to the earliest possible priority date of the '661 patent.

C. Terlevich (Ex-1009)

99. Terlevich is a journal article published in 2003. (Ex-1024 at ¶105.) I understand Terlevich is prior art to the '661 patent irrespective of its earliest possible priority date.

100. Terlevich is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

101. Terlevich discloses “hypophosphataemia associated with refeeding

syndrome requires treatment with intravenous phosphate 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 [500-mL] semi-rigid cylindrical polyethylene container, with a twist-off seal at one end and a ring tab at the other” and each “500-mL PPF contains 50 mmol phosphate, 81 mmol sodium and 9.5 mmol potassium.” (*Id.* at 1326.)

D. Ogawa (Ex-1010)

102. Ogawa is a journal article published in 2013. (Ex-1024 at ¶105.) I understand Ogawa is prior art to the ’661 patent irrespective of its earliest possible priority date.

103. Ogawa is in the same field of endeavor as the ’661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

104. Ogawa conducted studies that showed less than 50 ppb of aluminum should be used in parenteral phosphate buffer solutions to avoid particle formation. (Ex-1010 at 544-45.)

E. Nevakar (Ex-1011)

105. Nevakar is U.S. Patent Application Publication No. 2019/0290602 published September 26, 2019. (Ex-1011; Cover.) I understand Nevakar is prior art to the '661 patent irrespective of its earliest possible priority date.

106. Nevakar is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

107. Nevakar discloses that “storage stable ready-to-administer composition[s] containing an oxygen-sensitive drug,” 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.)

F. NEXCEL (Ex-1012)

108. NEXCEL is a June 2023 product data sheet to the bag film materials referenced in Table 20 of the '001 application. (Ex-1023 at 24-26.) I understand NEXCEL is prior art if the '661 patent is not entitled to claim priority to the '001 application.

109. NEXCEL is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

110. NEXCEL is referenced in Table 20 of the '001 application as being a type of bag film material.

G. Nema (Ex-1013)

111. Nema is a textbook published in 2010. (Ex-1024 at ¶105.) I understand Nema is prior art to the '661 patent irrespective of its earliest possible priority date.

112. Nema is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

113. The Nema reference includes chapters 5 and 12 from the textbook entitled "*Pharmaceutical Dosage Forms: Parenteral Medications*, Third Edition, Volume 1: Formulation and Packaging."

114. Chapter 5 entitled "*Formulation development of small and large volume injections*" discloses various well known principles surrounding parenteral solutions, including tonicity requirements.

115. Chapter 12 entitled "*Plastic packaging for parenteral drug delivery*" discloses various well known principles surrounding parenteral packaging, including packaging for both small and large volume parenteral (SVP, LVP) solutions and the importance of minimizing moisture penetration, such as by using multilayer polyolefin containers.

H. Rowe (Ex-1014)

116. Rowe is a textbook published in 2009. (Ex-1024 at ¶105.) I understand Rowe is prior art to the '661 patent irrespective of its earliest possible priority date.

117. Rowe is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

118. The Rowe reference entitled "Handbook of Pharmaceutical excipients" discloses well known information about sodium chloride, sodium phosphate (dibasic), and sodium phosphate (monobasic).

I. ISMP (Ex-1015)

119. ISMP is a Canadian Safety Bulletin published in 2006. (Ex-1023 at 57-59.) I understand ISMP is prior art to the '661 patent irrespective of its earliest possible priority date.

120. ISMP is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

121. ISMP discloses information on intravenous potassium phosphate solutions, including what issues can arise during on-site preparation of doses for intravenous infusion.

J. Brunelli (Ex-1019)

122. Brunelli is a journal article published in 2006. (Ex-1024 at ¶105.) I understand Brunelli is prior art to the '661 patent irrespective of its earliest possible priority date.

123. Brunelli is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

124. Brunelli discloses information on intravenous potassium phosphate solutions, including to apply a weight and serum phosphate-based approach when administering intravenous potassium phosphate solutions.

K. Wadsworth (Ex-1026)

125. Wadsworth is a journal article published in 2016. (Ex-1024 at ¶105.) I understand Wadsworth is prior art to the '661 patent irrespective of its earliest possible priority date.

126. Wadsworth is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

127. Wadsworth discloses information on intravenous potassium phosphate solutions, including information relating to the Phosphates Polyfusor® described by Terlevich.

L. Perks (Ex-1030)

128. Perks is a journal article published in 2017. (Ex-1024 at ¶105.) I understand Perks is prior art to the '661 patent irrespective of its earliest possible priority date.

129. Perks is in the same field of endeavor as the '661 patent relating to parenteral solutions for intravenous administration to a patient and/or ready-to-use packaging for the same.

130. Perks conducted studies on phosphate solutions having 3 mmol/100 ml or 15 mmol/100 ml phosphate in PVC bags.

M. The Conventional Packaging References (Exs. 1031-37)

131. Exhibits 1031-37 are prior art patents or printed publications relating to conventional medical grade packaging for intravenous solutions. These references are in the same field of endeavor as the '661 patent relating to ready-to-use packaging for intravenous solutions.

VIII. CLAIM CONSTRUCTION

132. It is my understanding that in order to properly evaluate the '661 patent, the terms of the claims must first be interpreted. It is my understanding that for the purposes of this inter partes review, the claims are to be construed under the so-called *Phillips* standard, under which claim terms are given their ordinary and customary meaning as would have been understood by one of ordinary skill in the

art in light of the specification and prosecution history, unless the inventor has set forth a special meaning for a term. For the purposes of this declaration, it is my opinion that none of the claim terms requires a specific construction, and all will be given their plain and ordinary meaning.

IX. THE '661 PATENT IS NOT ENTITLED TO CLAIM PRIORITY TO THE '001 APPLICATION

133. As explained previously, I understand the '661 patent claims priority to two prior applications: the '001 application and the '518 provisional:

“Related U.S. Application Data

“(63) Continuation-in-part of application No. 17/499,001, filed on Oct. 12, 2021, now U.S. Patent No. 11,813,291.

“(60) Provisional application No. 63.090,518, filed on Oct. 12, 2020.”

(Ex-1001, (63), (60) [page 1].)

134. For the below reasons, the '001 application fails to provide written description support for a phosphorous range of between 1.5 mmol/100 ml and 15 mmol/100 ml (the “Phosphorous Range”), as required by every independent claim of the '661 patent. The '518 provisional also fails to provide written description support for the claimed Phosphorous Range.

A. Legal Background On Priority and Written Description Support

135. I understand from counsel that, for a claim in a later-filed patent application to be entitled to the filing date of an earlier patent application, that earlier

patent application must provide written description support for the claim. Accordingly, for the '661 patent to claim priority to the '001 application, the specification of the '001 application must provide written description support for the claims of the '661 patent, including the claimed Phosphorous Range.

136. I further understand from counsel that, to satisfy the written description requirement, the disclosure of the application relied upon must reasonably convey to a POSITA that the inventor had possession of the claimed subject matter as of the filing date.

137. I further understand from counsel that written description support cannot be based on what is obvious. Instead, the disclosure in the prior application must allow a POSITA to immediately discern the limitation at issue in the claims.

B. The RTU phosphorous disclosures of the '001 application

138. All independent claims require a ready-to-use ("RUT") solution having between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous (the "Phosphorous Range"):

1. A sterile ready-to-use aqueous potassium solution,...wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous...."

11. A sterile ready-to-use premixed pharmaceutical product...wherein the pharmaceutical product comprises a potassium phosphates in an

aqueous sodium chloride solution containing...(b) between about 1.5 mmol/100 ml and 15 mmol/100 ml phosphorus....”

“17. A method...comprising: administering, without prior dilution, a sterile, and ready-to-use solution...wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus....”

(Ex-1001 at claims 1, 11, 17.)

139. The '001 application discloses a single phosphorous concentration for its RTU solutions: 15 mmol/100 ml. This is shown by the following disclosures of the '001 application:

“A ready-to-use (RTU) potassium phosphates in sodium chloride solution for phosphorus replacement therapy includes 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-1006 at Abstract.)

“In one aspect of the inventive subject matter, the inventors contemplate an isotonic sterile ready-to-use (RTU) aqueous potassium phosphates solution that comprises potassium phosphates and sodium chloride, wherein the solution includes 15 mmol/100 ml phosphorus (0.15 mmol/mL) and equal or less than 50 mcg/L aluminum.” (*Id.* at 0010.)

“While not limiting to the inventive subject matter, the pharmaceutical product may include potassium phosphates in an aqueous sodium chloride solution, containing (a) less than 50 mcg/L aluminum, (b)

about 15 mmol/100 ml phosphorus, and (c) about 22 mEq/100 mL potassium.” (*Id.* at 0013.)

“The premixed pharmaceutical product in the flexible polymeric container preferably has a volume of 100 mL, and it is further preferred that the flexible polymeric container is enclosed in a secondary metallized overwrap. Therefore, in some embodiments, the premixed pharmaceutical product will comprise about 4.65 mg/mL of phosphorus (0.15 mmol/mL), about 8.50 mg/mL of potassium (0.22 mEq/mL), about 3.57 mg/mL of sodium, and about 5.43 mg/mL of chloride.” (*Id.* at 0015.)

“Most typically, the solution comprises about 15 mmol/100 ml phosphorus, about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum. In further contemplated embodiments, the rate of infusion is 6.8 mmol phosphates per hour or 15 mmol phosphates per hour, and/or the route of administration is a central venous catheter.” (*Id.* at 0016.)

“For example, 100 mL of the RTU solution may be packaged into a flexible polymeric container to thereby provide in a sodium chloride solution about 15 mmol total phosphates and about 22 mEq potassium for injection, wherein the RTU solution has equal or less than 50 micrograms/liter (mcg/L or µg/L) aluminum.” (*Id.* at 0028.)

“Therefore, especially preferred premixed pharmaceutical products that provide a desirable phosphates to potassium ratio will be prepared such that the solution will contain in water 11.2 KH₂PO₄ and 11.8 mg/mL K₂HPO₄ for a total 0.15 mmol/mL of phosphates, and 9 mg/mL sodium chloride.” (*Id.* at 0029.)

“In more typical embodiments, the premixed or ready-to-use stable pharmaceutical, formulation of potassium phosphates in sodium chloride at 15 mmol/100 ml of Phosphorus is packaged in a non-PVC plastic container with ports and container closure systems, which is terminally sterilized at a temperature of at least about 110° C to 130° C via autoclaving with a dwelling time ranging from 7 to 30 minutes.” (*Id.* at 0036.)

“ As the flexible container comprises a fixed volume (e.g., 100 ml) of the sterile RTU potassium phosphates in sodium chloride solution includes 15 mmol/100 ml Phosphorus, administration to adult or pediatric patients by peripheral venous catheter or central venous catheter may be readily accomplished based on programming the infusion rate accordingly.” (*Id.* at 0043.)

“Formulation of ingredients for potassium phosphates in sodium chloride injection 15 mmol/100 ml solution....For a 15 mmol/100 ml concentration of phosphorus, 11.2 mg/mL KH₂PO₄ and 11.8 mg/mL K₂HPO₄ are added to water with mixing as disclosed herein. The deionized water is to volume (quantum satis (Q. S.)), which for the ready-to-use (RTU) formulation disclosed herein, is fixed at 100 ml. Sodium chloride (NaCl) is an admixture carrier and tonicity agent having a IIG limit of 0.9" weight/volume (w/v). Accordingly, for a 100 ml solution, 900 mg of NaCl is added.” (*Id.* at 0046.)

“Table 3: Formulation of potassium phosphates in sodium chloride injection solution (15 mmol/100 ml of Phosphorus and 22 mEq/100 mL of Potassium)” (*Id.* at 0047.)

“Table 4: Batch formulation of potassium phosphates injection solution (15 mmol/100 ml of Phosphorus and 22 mEq/100 mL of Potassium) in 1 liter (1000 ml). Formulation for Bulk solution of Potassium Phosphates in Sodium Chloride Injection, RTU.” (*Id.*)

“Table 8: Specification of Potassium Phosphates in Sodium Chloride Injection, RTU... 9. Assay of Phosphorous (Label Claim: Each 100 mL bag contains 4.65 ml/mL [15 mmol/100 ml] of Phosphorous) (*Id.*)

“Thus, the solution contained 15 mmol/100 ml phosphorus (0.15 mmol/mL), 22 mEq/100 mL potassium, and had an aluminum content of about 30 mcg/L. Table 20 provides an overview of the packaging materials used and filling/autoclaving conditions employed.” (*Id.* at 0081.)

“TABLE 20 Potassium Phosphates in Sodium Chloride Injection (15 mmol/100 mL of Phosphorus and 22 mEq/100 mL of Potassium)” (*Id.*)

As shown above, every disclosure of the '001 application's specification is to an RTU solution having a phosphorous content of 15 mmol/100 ml. No other RTU concentrations are disclosed.

140. The original claims of the '001 application also only disclose a RTU solution with 15 mmol/100 ml phosphorous:

“1. An isotonic sterile ready-to-use (RTU) aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride, wherein the solution comprises 15 mmol/100 ml phosphorus (0.15 mmol/mL) and equal or less than 50 mcg/L aluminum.

11. A sterile ready-to-use (RTU) 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) about 15 mmol/100 ml phosphorus, and (c) about 22 mEq/100 mL potassium.

16. The pharmaceutical product of claim 11, wherein the premixed pharmaceutical product comprises about 4.65 mg/mL of phosphorus (0.15 mmol/mL), about 8.50 mg/mL of potassium (0.22 mEq/mL), about 3.57 mg/mL of sodium, and about 5.43 mg/mL of chloride.

17. A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising: administering, without prior dilution, an isotonic, sterile, and ready-to-use (RTU) 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 about 15 mmol/100 ml phosphorus, about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum.” (Ex-1006 at claims 1, 11, 16, 20.)

141. Based on these disclosures, POSITA would have concluded that the '001 application discloses a single phosphorus concentration for its RTU solutions: 15 mmol/100 ml.

142. I have also reviewed the '518 provisional application to determine whether it discloses anything other than a 15 mmol/100 ml. I have concluded that it

does not because it generally includes the same disclosures as that of the '001 application as it relates to the RTU solution phosphate concentration. (Ex-1005 at 15 (Abstract), 16 (claim 1), 17 (claims 10, 13-14), 18 (claim 17, amount of KMP+KDP is 15 mmol/100 ml), 19 (claims 24, 27), 22-28 (0011, 0014-17, 0027, 0030-31, 0033, 0035), 30 (0041-43), 37 (Table 6, specification for assay of phosphorous content).)

143. Thus, a POSITA would have also concluded that the '518 provisional also discloses a single phosphorus concentration for its RTU solutions: 15 mmol/100 ml.

C. The '001 application fails to disclose the claimed Phosphorous Range

144. As shown above, the '001 application only discloses an RTU solution with a phosphorous concentration of 15 mmol/100 ml. However, all Challenged Claims require the claimed Phosphorous Range, i.e., between 1.5 mmol/100 ml and 15 mmol/100 ml, which range is only disclosed in the '661 patent. Thus, it is my opinion that the '001 patent fails to disclose the claimed Phosphorous Range. Accordingly, I understand that the '661 patent cannot claim priority to the '001 application, meaning the effective filing date of the '661 patent is its actual filing date of September 5, 2023.

145. I understand from counsel that Patent Owner has argued that the below disclosures of the '001 application provide written description support for the

claimed Phosphorous Range because those disclosures recite “not more than” various amounts of potassium phosphate.

“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.

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 of age and older and not more than 5.5 mmol/100 ml in pediatric patients less than 12 years of age.” (Ex-1006 at ¶¶0044-45.)

I disagree. The “not more than” disclosures of these paragraphs do not convey possession of the claimed Phosphorous Range for at least the below reasons.

146. First, the “not more than” disclosures cited above do not relate to the concentration of phosphorous in the RTU solution. Instead, these disclosure clearly

relate to the daily maximum amount of phosphates that may be administered, centrally or peripherally, to different age groups. This is shown by the Background of the '001 application, which includes Table 1 and the following text:

“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))”

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)

(Ex-1006 at 0005.) As the Background of the '001 application clearly shows, the “not more than” disclosures of paragraphs 0044-45 of the '001 application are the maximum recommended daily concentration of potassium phosphate by age and route of administration. The below table compares the two disclosures.

'001 application: Table 1: Maximum <u>Daily</u> Concentrations	'001 application: ¶¶0044-45 disclosures
Peripheral Venous: 6.8 mmol/100 ml	“not more than 6.8 mmol/100 ml in adult patients”
Central Venous: 18 mmol/100 ml	“not more than 18 mmol/100 ml in adult patients”
Peripheral Venous: 0.27 mmol/10 ml	“not more than 2.7 mmol/100 ml in

(or 2.7 mmol/100 ml)	pediatric patients less than 12 years of age.”
Central Venous: 0.55 mmol/10 ml (or 5.5 mmol/100 ml)	“not more than 5.5 mmol/100 ml in pediatric patients less than 12 years of age”

Thus, the “not more than” disclosures of paragraphs 0044-45 of the ’001 application are not disclosures of the amount of phosphate in the RTU solution.

147. My opinions on this are confirmed by the ’518 provisional application, which includes the same paragraphs of the ’001 application, but with the “maximum daily” language included:

“[0036] 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 maximum daily 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.

[0037] 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 maximum daily concentration of phosphates administered by central venous catheter is

not more than 18 mmol/100 ml in adult patients or pediatric patient 12 years of age and older and not more than 5.5 mmol/100 ml in pediatric patients less than 12 years of age.” (Ex-1006 at ¶¶0044-45.)

(Ex-1005 at 28-29.)

148. For the above reasons, a POSITA would not understand the “not more than” disclosures of paragraphs 0044-45 of the ’001 application to be a disclosure of the phosphate concentration of the sterile, RTU phosphate solutions themselves; instead, a POSITA would know that these disclosures relate to the daily maximum phosphate concentrations allowed for adult or pediatric patients depending on whether the administration was via peripheral venous or central venous administration.

149. Second, even if the above “not more than” disclosures did constitute a disclosure of phosphate concentrations for the sterile, RTU solutions (they do not), such disclosures still fail to disclose the claimed Phosphorous Range. At best, these disclosures constitute a range of from more than zero to the stated maximum limit, depending on the patient’s age and whether the administration is peripherally or centrally, i.e. the following ranges:

“from >0 to 6.8 mmol/100 ml;” or

“from >0 to 18 mmol/100 ml;” or

“from >0 to 2.7 mmol/100 ml;” or

“from >0 to 5.5 mmol/100 ml.”

Such ranges do not specifically disclose the claimed Phosphorous Range. Instead, such ranges only overlap with the claimed Phosphorous Range, shown below.

Alleged “range” of phosphorous in ¶¶0044-45 of the ’001 application	Claimed Range
“from >0 to 6.8 mmol/100 ml”	“between 1.5 mmol/100 ml and 15 mmol/100 ml”
“from >0 to 18 mmol/100 ml”	
“from >0 to 2.7 mmol/100 ml”	
“from >0 to 5.5 mmol/100 ml”	

150. Here, a POSITA cannot instantly discern the claimed range from any of these overlapping ranges. Indeed, neither 1.5 mmol/100 ml nor 15 mmol per 100 ml is recited in any of these ranges. Accordingly, even if the “not more than” disclosures were disclosures of a concentration of the premixed RTU solution, they do not provide written description support for the claimed Phosphorous Range.

151. I further note that the ’661 patent considers the phosphorous concentration *to be critical* such that even a 1-5% change in concentration is significant.

“Moreover, the solution may have, 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*, and/or the solution may have, after autoclaving and storage of at least 3 months at 25° C and 40% relative humidity....” (Ex-1001 at 3:45-51.)

“Alternatively, or additionally, the solutions may have, after autoclaving and storage of at least 3 months at 25° C and 40% relative humidity, *a change in phosphorus* and/or potassium *content of no more*

than $\pm 3\%$ (*absolute*), or no more than $\pm 2.5\%$ (*absolute*), or no more than $\pm 2.0\%$ (*absolute*), or no more than $\pm 1.5\%$ (*absolute*), or no more than $\pm 1.0\%$ (*absolute*), or no more than $\pm 0.8\%$ (*absolute*), or no more than $\pm 0.6\%$ (*absolute*), relative to initial conditions.” (*Id.* at 8:55-62.)

“Table 8: Specification of Potassium Phosphates in Sodium Chloride Injection, RTU ... 9. Assay of Phosphorus (Label Claim: Each 100 mL bag contains 4.65 mg/mL [15 mmol/100 ml] of Phosphorus)... Release Specification...Not less than 95% and Not more than 105%....”³ (*Id.* at Cols. 13-14, Table 8)”

152. Accordingly, even if the “not more than” disclosures were considered to be a *maximum* phosphorous concentration of the sterile RTU solution (they are not), the highest and lowest concentrations allowed by the ’661 patent itself would be as per the below table.

Not more than disclosures of the ’001 application	$\pm 5\%$ Tolerance
“not more than 6.8 mmol/100 ml”	6.46-7.15 mmol/100 ml
“not more than 18 mmol/100 ml”	17.1-18.9 mmol/100 ml
“not more than 2.7 mmol/100 ml”	2.565-2.835 mmol/100 ml
“not more than 5.5 mmol/100 ml”	5.225-5.775 mmol/100 ml

None of these disclosures, therefore, would have been considered to be a disclosure

³ A POSITA would understand these disclosures to be equivalent to a requirement of $\pm 5\%$ relative to the target concentration of 15 mmol/100 ml.

of a lower limit of the claimed Phosphorous Range, let alone a disclosure of a lower limit of 1.5 mmol/100 ml as required by the claimed Phosphorous Range.

153. A POSITA, therefore, would not consider the '661 patent's disclosure of "not more than 2.7 mmol/100 ml" (or any of the other "not more than" disclosures) to disclose a concentration of "1.5 mmol/100 ml of phosphorous."

154. In the interest of completion, I note that claim 11 recites "between about 1.5 mmol/100 ml and 15 mmol/100 ml phosphorus." But, as provided above, the '661 patent allows, at most, a 5% deviation from its target phosphorous concentration. Accordingly, "about 1.5 mmol/100 ml" reads on, at best, from 1.425 to 1.575 mmol/100 ml phosphorous (a change of 5% as compared to 1.5 mmol/100 ml), which is far removed from even the "not more than" disclosures of the '001 application discussed above. Thus, use of the word "about" in claim 11 does not alter my opinions—the '001 application fails to provide written descriptions support for the claimed Phosphorous Range irrespective of the use of the word "about."

D. The new RTU phosphorous disclosures of the '661 patent

155. I understand the '941 application, which resulted in the '661 patent, was filed as a "continuation-in-part" of the '001 application. I understand from counsel that a continuation-in-part application typically includes new matter relative to the prior application. I find that to be the case here.

156. Specifically, I have reviewed a redline comparison between the text of

the '941 application and the text of the '001 application. (Ex-1020.) As shown in that redline, many of the disclosures of the '941 application and the '001 application are the same. However, unlike the '001 application, the '941 application includes the following additional disclosures as it relates to the phosphorous content of its RTU solutions:

“Ready-to-use (RTU) potassium phosphates solutions for phosphorus replacement therapy are presented that include potassium phosphate and sodium chloride at a fixed volume with 1.5 to 15 mmol/100 mL phosphorus, no more than 22 mEq/100 mL potassium and less than 50 mcg/L aluminum.” (Ex-1002 at 155 (Abstract).)

“In still further experiments, the inventors explored further formulations with phosphorus concentration ranges of between 0.015 and 0.15 mmol/mL.” (Ex-1002 at 145 (0089).)

“For example, in some experiments, the inventors also tested formulations having a ten-fold lower phosphorus concentration, and in particular solutions comprising potassium phosphates and sodium chloride in which the solution comprised 1.5 mmol/100 ml phosphorus (0.015 mmol/mL) and equal or less than 50 mcg/L aluminum.” (*Id.* at 145-46 (0090).)

As shown, the claimed Phosphorous Range (i.e., between 1.5 mmol/100 ml and 15 mmol/100 ml) is first disclosed in the '941 application. This further confirms my opinions that the '001 application fails to disclose the claimed Phosphorous Range.

X. CLAIMS 1-20 ARE UNPATENTABLE

157. I have been asked to provide my opinion as to whether the Challenged Claims of the '661 patent would have been anticipated or obvious in view of the prior art. The discussion below provides a detailed analysis of how the prior art references identified below teach the limitations of the Challenged Claims of the '661 patent.

158. As part of my analysis, I have considered the scope and content of the prior art and any differences between the alleged invention and the prior art. I describe in detail below the scope and content of the prior art, as well as any differences between the alleged invention and the prior art, on an element-by-element basis for each Challenged Claims of the '661 patent.

159. As described in detail below, the alleged invention of the Challenged Claims would have been obvious in view of the teachings of the identified prior art references as well as the knowledge of a POSITA.

Grounds	Claim(s)	Basis
#1	1-20	Anticipated or rendered obvious by Nivagen-1 (Ex-1006)
#2	1-8, 11-13, 17-20	Rendered obvious by the CMP Art (i.e., "CMP-PCT"/Ex-1007 and "CMP-FDA"/Exs. 1008, 1027)) in view of Terlevich (Ex-1009), optionally in view of Ogawa (Ex-1010)
#3	9-20	The Ground 2 art in view of Nevakar (Ex-1011).

A. Ground 1: Nivagen-1 discloses every limitation of claims 1-20**1. Summary of Ground 1**

160. Ground 1 relies on Nivagen-1, which is the parent application to the '661 patent. As shown below, Nivagen-1 discloses all limitations of claims 1-20 of the '661 patent.

2. Challenged Claims

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

[1.1] wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous and,

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

161. Nivagen-1 discloses limitations 1.0, 1.1 and 1.2:

“In one aspect of the inventive subject matter, the inventors contemplate an isotonic sterile ready-to-use (RTU) aqueous potassium phosphates solution that comprises potassium phosphates and sodium chloride, wherein the solution includes 15 mmol/100 ml phosphorus (0.15 mmol/mL) and equal or less than 50 mcg/L aluminum.” (Ex-1006 at 0010; *see also id.* at 0002, 0009, 0013, 0015-16, and 0027-29, 0036, 0046, 0081, Tables 3-4 and 20, claims 1 and 16.)

As shown, Nivagen-1 discloses limitations 1.0 and 1.2 verbatim.

162. As for limitation 1.1, Nivagen-1 discloses that its RTU “solution includes 15 mmol/100 ml phosphorus,” which is the upper limit of the claimed Phosphorous Range (15 mmol/100 ml). It is my understanding from counsel that

the disclosure of an endpoint of a claimed range is a disclosure of that range.

163. In any event, the claimed range is also obvious to a POSITA because Nivagen-1 teaches an RTU solution having 15 mmol/100 ml, which overlaps with the claimed range of 1.5-15 mmol/100 ml. I understand from counsel that an overlap between a prior art range and a claimed range means the claimed range is *prima facie* obvious.

164. Thus, Nivagen-1 discloses or renders obvious these limitations.

[1.3] wherein the solution has a pH of between 6.2 and 6.8⁴

165. Nivagen-1 exactly discloses this limitation:

“Preferably, but not necessarily, sodium chloride is present in the solution in an amount of about 900 mg/100 ml, and/or the solution has a pH of between 6.2 and 6.8.” (Ex-1006 at 0011; *see also id.* at claim 5; Table 8 (showing many solutions having a pH between 6.2 and 6.8).)

166. Accordingly, Nivagen-1 discloses all limitations of claim 1, thereby anticipating or rendering obvious claim 1.

[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.

167. Nivagen-1 discloses this limitation:

⁴ I understand that a certificate of correction to the '661 patent was issued, correcting the pH range of claim 1 to that which is shown here. (Ex-1002 at 4.)

“In some embodiments, the potassium phosphates comprise potassium dihydrogen phosphate (KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4), wherein the *potassium dihydrogen phosphate is present in the solution an amount of* about 1,120 mg/100 ml **(8.2 mmol/100 ml)** phosphorus wherein the *potassium hydrogen phosphate is present in the solution in an amount of* about 1,180 mg/100 ml **(6.8 mmol/100 ml)** *phosphorus....*” (Ex-1006 at 0011; *see also id.* at 0029, 0032, 0038, 0046, 0081, claims 2, 12.)

168. As shown, Nivagen-1 discloses a molar ratio of 1.2 (KDP:KMP) per 100 ml ($8.2/6.8 = 1.2$), which lies within the claimed range. Thus, Nivagen-1 anticipates or renders obvious claim 2.

[Claim 3] The solution of claim 2, wherein the [KDP] is present in the solution an amount of between about 112 mg/100 ml and about 1,120 mg/100 ml and wherein the [KMP] is present in the solution in an amount of between about 118 mg/100 ml and about 1,180 mg/100 ml.

169. Nivagen-1 discloses this limitation. Specifically, as shown in claim 2, above, Nivagen-1 discloses its solutions may include about 1,120 mg/100 ml KDP and about 1,180 mg/100 ml KMP. (Ex-1006 at 0011; *see also id.* at 0029, 0032, 0038, 0046, 0081, claims 2, 12.) These amounts correspond to the endpoints of the claimed ranges, which I understand means the ranges of claim 3 are anticipated or rendered obvious.

[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.

170. Nivagen-1 discloses this limitation:

“In some embodiments...potassium is present in the solution in an amount of about 22 mEq/100 mL.” (Ex-1006 at 0011; *see also id.* at 0013, 0015-16, 0028, 0081, Tables 3-4 and 20, claims 1, 11, and 16-17.)

Thus, Nivagen-1 discloses the endpoint of the claimed ranges, which I understand means the range of claim 4 is anticipated or rendered obvious.

[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.

171. Nivagen-1 discloses this limitation:

“Preferably, but not necessarily, sodium chloride is present in the solution in an amount of about 900 mg/100 ml.” (Ex-1006 at 0011; *see also id.* at 0014, 0032, 0038, 0046, 0081, Table 3 and 20, claims 4 and 13.)

Thus, Nivagen-1 discloses the endpoints of the claimed range, which I understand means the range of claim 5 is anticipated or rendered obvious.

[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 25 micrometer size, respectively.

[Claim 7] The solution of claim 1,... a change in phosphorus of no more than 1% absolute.

[Claim 8] The solution of claim 1,...a change in potassium of no more than 2% absolute.

172. Nivagen-1 discloses claims 6-8:

“[T]he solution may have, 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. Moreover, the solution may have, 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, and/or the solution may have, 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.” (Ex-1006 at 0012; *see also id.* at 0015, 0042, claims 6-8.)

Thus, Nivagen-1 anticipates or renders obvious claims 6-8.

[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.

173. As shown, claim 9 includes one mandatory limitation and two optional limitations (volume and multilayer). Nivagen-1 discloses all limitations. Paragraph 12 of Nivagen-1 discloses the first two limitations:

“[T]he solution is packaged in a flexible (e.g., polyolefin) container, typically at a volume of 100 mL, and the flexible polyolefin container may further be contained in a secondary metallized overwrap.” (Ex-1006 at 0012; *see also id.* at 0015, 0018, 0035, 0081, Table 20, FIG. 1, claims 9 and 14.)

174. Nivagen-1, Table 20 discloses the final limitation (“flexible multilayer bag”). Specifically, Table 20 discloses several “Bag Source[s]” and “Bag Film Material[s],” including the material “NEXCEL M312 Film (Sealed Air) 135 x 0.40.”

(Ex-1006 at Table 20.) NEXCEL M312 films are “clear, 5-layer, polyolefin” materials. (Ex-1012 at 1; Ex-1023 at 25.)

175. Thus, Nivagen-1 discloses all limitations, mandatory or optional, thereby anticipating and rendering obvious claim 9.

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

176. Nivagen-1 discloses this limitation:

“[T]he solution is packaged in a flexible (e.g., polyolefin) container, typically at a volume of 100 mL, and the flexible polyolefin container may further be contained in a secondary metallized overwrap.” (Ex-1006 at 0012; *see also id.* at 0015, 0034, claim 10, 15.)

Thus, Nivagen-1 anticipates or renders obvious claim 10.

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

177. Nivagen-1 discloses a “sterile ready-to-use...pharmaceutical product stored in a flexible polymeric container” for the reasons provide above relative to limitation 1.0 and claim 9. Nivagen-1 also discloses that its RTU solutions are premixed:

“Therefore, in still further contemplated aspects, the inventors contemplate a sterile ready-to-use (RTU) premixed pharmaceutical product stored in a flexible polymeric container.” (Ex-1006 at 0013, *see also id.* at 0015, 0029, 0036, claims 11, 14, 16.)

Thus, Nivagen-1 discloses this 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,

178. Nivagen-1 discloses this limitation for the reasons provide above relative to limitations 1.0 and 1.2.

[11.2] (b) between about 1.5 mmol 100 ml and 15 mmol/100 ml phosphorus, and,

179. Nivagen-1 discloses this limitation for the reasons provide above relative to limitation 1.1.

[11.3] (c) no more than about 22 mEq/100 mL potassium.

180. Nivagen-1 discloses this limitation for the reasons provide above relative to claim 4.

181. Accordingly, Nivagen-1 discloses all limitations of claim 11, thereby anticipating or rendering obvious claim 11.

[Claim 12] The pharmaceutical product of claim 11....

182. Claim 12 is disclosed by Nivagen-1 for the reasons provided above relative to claims 2-3. Thus, Nivagen-1 anticipates or renders obvious claim 12.

[Claim 13] The pharmaceutical product of claim 12....

183. Nivagen-1 discloses this limitation for the reasons provide above relative to claim 5. Thus, Nivagen-1 anticipates or renders obvious claim 13.

[Claims 14-16] The pharmaceutical product of....

184. Nivagen-1 discloses the limitations of claims 14-15 for the same

reasons provide above relative to claim 9, and Nivagen-1 discloses the limitations of claim 16 for the same reasons provide above relative to claim 10. Thus, Nivagen-1 anticipates or renders obvious claims 14-16.

[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, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container

[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;

185. Nivagen-1 discloses these limitations:

“[T]he inventors also contemplate a method of administering phosphates to a patient in need of phosphorus replacement therapy, ...include[ing] a step of administering, without prior dilution, an isotonic, sterile, and ready-to-use (RTU) 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.” (Ex-1006 at 0016; see also *id.* at 0009-10, 0013, 0030, 0043-45, claim 17.)

Thus, Nivagen-1 discloses these limitations.

[17.2] wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus,

186. Nivagen-1 discloses this limitation for the reasons provide above

relative to limitation 1.1.

[17.3] no more than about 22 mEq/100 mL potassium, and

187. Nivagen-1 discloses this limitation for the reasons provide above relative to claim 4.

[17.4] less than 50 mcg/L aluminum.

188. Nivagen-1 discloses this limitation for the reasons provide above relative to limitation 1.2.

189. Accordingly, Nivagen-1 discloses all limitations of claim 17, thereby anticipating or rendering obvious claim 17.

[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 or peripheral 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.

190. Nivagen-1 discloses these limitations:

“Most typically, the solution comprises about 15 mmol/100 ml phosphorus, about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum. In further contemplated embodiments, the rate of infusion is 6.8 mmol phosphates per hour or 15 mmol phosphates per hour, and/or the route of administration is a central venous catheter. Furthermore, it is contemplated that the solution can be administered after extended storage (e.g., storage for at least 3 months at 25° C and

40% relative humidity). (Ex-1006 at 0016; *see also id.* at 0028, 0030, 0041-43, 0045, Tables 1-2, claims 18-20.)

Thus, Nivagen-1 anticipates or renders obvious claims 18-20.

B. Ground 2: The CMP Art in view of Terlevich, optionally in view of Ogawa, teaches claims 1-8, 11-13, 17-20

1. Summary of Ground 2

191. Ground 2 relies on the CMP Art for most limitations of the Challenged Claims. As I show below, it was also obvious to combine the CMP Art with itself and with Terlevich, which discloses ready-to-use parenteral potassium phosphate solutions. As I also show below, it was also obvious to combine the teachings of the CMP Art and Terlevich with Ogawa, which discloses to use <50 ppb Al to avoid precipitation of insoluble particles in potassium phosphate buffer solutions, such as those described by CMP-PCT.

2. Reasons to Combine the Ground 2 Art

192. A POSITA would have been motivated and found it obvious to combine the teachings of the CMP Art, Terlevich and Ogawa for the reasons provided below.

193. 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.)

194. CMP-PCT describes two different sterile potassium phosphate

solutions for injection. The first includes 175 mg/mL of KMP and 300 mg/mL of KDP. CMP-PCT calls these solutions the “first embodiment” or the “second embodiment” solutions, the only difference being the first embodiment comprises the listed ingredients whereas the second embodiment consists of the listed ingredients.⁵ (*Id.* at 2:29-3:4.) The second sterile potassium phosphate solution for injection is a KMP only solution, which CMP refers to as the “third embodiment” or “fourth embodiment.” (*Id.* at 7:18-25.) I do not rely on the KMP only solution in my analysis—instead, I rely on the KMP:KDP solution described by CMP-PCT.

195. CMP-PCT discloses that the first or second embodiment solutions may be administered to treat “hypophosphatemia in a patient in need thereof.” (*Id.* at 4:23-5:3.)

196. As CMP-PCT explains, prior to its alleged invention, a prior potassium phosphates injection solution contained “a mixture of [KMP] and [KDP] in water,” which solution contained 224 mg of KMP and 236 mg of KDP per milliliter of solution. (*Id.* 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.

⁵ I understand from counsel that “comprising” is a term of art in patent law and is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended, and does not exclude additional, unrecited elements.

(*Id.* at 2:15-16.) The inventors solved the particulate problem 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 2:20-24.)

197. The CMP-PCT composition may achieve “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.)

198. CMP-PCT discloses that its solutions have very low levels of aluminum after extended storage, such as not more than 1 ppm when stored in a plastic vial at 4-8°C or even at room temperature:

“A tenth aspect of the first or second embodiment is directed to a plastic vial comprising the composition of the first or second embodiment ***having an aluminum content of not more*** than about 5 ppm, about 4 ppm, about 3 ppm, about 2 ppm, ***or about 1 ppm*** after ***storage at 4-8°C*** for 3-months, 6-months, 12-months, 18-months, 24-months, 36-months, or longer (e.g., 48-months). The plastic vial optionally comprises a coating comprised of SiO₂.

An eleventh aspect of the first or second embodiment is directed to a plastic vial comprising the composition of the first or second embodiment ***having an aluminum content of not more*** than about 5

ppm, about 4 ppm, about 3 ppm, about 2 ppm, **or about 1 ppm** after **storage at room temperature** for 3 -months, 6-months, 12- months, 18-months, 24-months, 36-months, or longer (e.g., 48-months). The plastic vial optionally comprises a coating comprised of SiO₂.” (*Id.* at 4:4-15.)

199. 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 produce (premix) and ship the CMP-PCT solutions as ready-to-use solutions.

200. Specifically, like CMP-PCT and the ’661 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,” “the 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 its 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% of cases achieving a serum phosphate concentration of > 0.50 mmol/L within 72 h.” (*Id.* at 1327.)

201. 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 of (10 mmol/100 ml) for direct administration to the patient without dilution. Wadsworth confirms as much:

A commonly used treatment is the Phosphate Polyfusor®, a solution containing 50 mmol PO_4^{3-} , 9.5 mmol K^+ , and 81 mmol Na^+ in 500 mL, given over 24 h via a central venous catheter. This preparation should be infused alone, via a dedicated port of a central line, and if given peripherally should have a dedicated cannula. Peripherally, the ideal is to reduce the rate of infusion due to risk of pain and phlebitis at the injection site, but with close monitoring could be given at the same rate as the central dose.” (Ex-1026 at 309.)

202. Perks further confirms that a concentration of 10 mmol/10 ml phosphate is suitable because it was typical for hospital pharmacies to prepare dilute

sodium phosphate solutions having a RTU phosphate concentration of from 3 mmol/100 ml to 15 mmol/100 ml:

“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.)

203. A POSITA would have been motivated to apply the RTU teachings of Terlevich to CMP-PCT. Both references are directed at treating hypophosphatemia with potassium phosphate solutions, with CMP-PCT disclosing concentrated solutions for later dilution and with Terlevich disclosing RTU solutions. 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.

“Premixed minibags eliminate the need for independent admixture preparation and provide significant time, labor saving and waste reduction advantages. Most major parenteral drugs are now available in this format, including drugs for antibiotic, analgesic, anticonvulsant,

cardiovascular, psychotherapeutic and respiratory preparations.” (Ex-1013 at 317-18.)

204. A RTU solution also helps avoid unnecessary calculations, and potential errors, by practitioners. As a ISMP Canada Safety Bulletin from 2006 explains:

“Product labels for commercially available potassium phosphates injection can be confusing because of the nature of the product (see Figure 1 for one example). 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.” (Ex-1015 at 1.)

205. Accordingly, a POSITA would have been motivated to produce the CMP-PCT solutions as RTU solutions based on the teachings of Terlevich.

206. A POSITA also would have had a reasonable expectation of success in preparing the CMP-PCT solutions as ready-to-use solutions, which were already known. Indeed, it would be straightforward for a POSITA to apply the teachings of Terlevich to CMP-PCT to achieve RTU solutions.

207. Terlevich teaches that its RTU solutions used 10 mmol/100 ml of phosphates for direct administration (Ex-1009 at 1326 (“[a] 500-mL PPF contains 50 mmol phosphate”)), and it would be obvious to make the CMP-PCT solutions at this diluted concentration while keeping the ratios 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.

208. Specifically, 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.

209. A POSITA would not expect any change in particulate levels when diluting the CMP-PCT solutions by a factor of 30 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.

210. As it relates to (a) (no particulates due to KMP and KDP amounts), as CMP-PCT explains, lower levels of KMP avoids particulate formation because its solubility is generally less than that of KDP:

“It was determined that the average solubility of KMP at about 23°C is 213 ± 35 mg/mL. The average KMP solubility is consistent with a reported KMP solubility in about 4.5 parts water. See, e.g., Merck Index (1976), Monograph No. 7446 at 7447. The reported solubility of KMP in about 4.5 parts water corresponds to a solubility of about 222 mg KMP per mL, but the Merck Index does not state the temperature of the reported solubility of KMP in about 4.5 parts water. The reported

solubility of about 222 mg KMP per mL is in general agreement with the reported solubility for KMP of 0.226 kg KMP per kg of water (or 226 mg/mL) at 20°C. See Mullin. As a point of reference, the marketed PPI products contain KMP at a concentration of 224 mg/mL. Thus, it can be seen that the amount of KMP in the [prior] marketed PPI product is close to the reported solubility limit for KMP when stored at about 20°C.

KDP is much more soluble in water, compared to KMP, with a KDP solubility of about 900 mg/mL. As a point of reference, the [prior] marketed PPI products contain KDP at a concentration of 236 mg/mL.

Based on the results from the above-mentioned experiments related to the test compositions coupled with the reported solubility values of KMP and KDP, it was believed that the concentration of KMP in the [prior] PPI products might be too high. It was hypothesized that the high concentration of KMP coupled with a failure to maintain control of storage conditions may contribute to the formation of visible particulates in marketed PPI products. In that regard, experiments were devised that evaluated potassium phosphate compositions having differing amounts of KMP and KDP.” (Ex-1007 at 13:17-14:5.)

211. Further, the examples of CMP-PCT show that lowered level of KMP prevents particulate precipitation while maintaining total phosphate concentration at 3 mmol phosphate/ml. (*Id.* at 14:6-17:8 (various KMP:KDP examples tested, with a 1 L solution having 175 g KMP and 300 g KDP anticipated to “provide a robust formulation ensuring solubility of KMP, and thus, preventing the formation of

undesirable visible particulates” but with “the same millimolar quantity of phosphate (i.e., 3 mmol phosphate/mL) as the marketed PPI products.”); *see also id.* 18:24-19:5 (examples showing no particulates due to new KMP+KDP concentration).)

212. As it relates to (b) (aluminum content), as I explained above, CMP-PCT already taught that aluminum should be avoided due to its toxicity. (*See* §VI.C, *supra.*) Accordingly, as I explained above, CMP-PCT desires not more than 1 ppm Al in its plastic vial embodiments, and even achieved about 0.2-0.3 ppm (200-300 ppb) in such embodiments:

“Tests conducted in a plastic vial (e.g., with a medical grade cyclic olefin polymer (COP) with or without a SiO₂ coating) on a composition of the first or second embodiment 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 a composition of the first or second embodiment stored in a plastic vial may be stored at room temperature.” (*Id.* at 20:1-7.)

213. As it relates to (c) (use of plastic vials), CMP-PCT teaches potassium phosphate solutions in glass vials leach aluminum:

“The initial aluminum assays for the aseptic glass vials (2.4 ppm) and terminal sterilized glass vials (5.8 ppm) shows that terminal sterilization is a source of aluminum in the composition. Additionally, aluminum continues to leach from the glass into the composition after storage for an extended period. The following table summarizes the

aluminum content for terminal sterilized glass vials stored at either 4-8°C or 25°C/60% RH, initially (0M), at 3-months (3M), at 12-months (12M), and at 18-months (18M).” (*Id.* at 19:6-12.)

214. Conversely, plastic vials did not show an increase in aluminum over time. (*Id.* at 20:1-7.) Accordingly, a POSITA would expect the RTU potassium phosphate solutions taught by the combination of CMP-PCT and Terlevich to be stable over long periods of time and without particulate issues when distributed in a plastic vial or similar plastic container.

215. For at least the above reasons, a POSITA would have been motivated to produce a RTU solution based on CMP-PCT but with 30 times lower KMP and KDP concentrations, as shown below:

- CMP-PCT teaches the use 175 mg/ml of KMP or 17,500 mg/100 ml; divide by 30 to achieve target RTU concentration (per Terlevich), which results in about 583 mg/100 ml or 4.28 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 30 to achieve target RTU concentration (per Terlevich), which results in 1000 mg/100 ml or 5.74 mmol/100 ml of KDP. (The molecular weight of KDP is 174.18 g/mol.)

216. Thus, a POSITA seeking to produce a RTU solution based on the teachings of CMP-PCT and Terlevich would have found it obvious (a) to produce a

solution having 4.28 mmol/100 ml KMP and 5.74 mmol/100 ml KDP for a total phosphate concentration of about 10 (10.02) mmol/100 ml, and (b) to store such RTU solutions in a suitable pharmaceutical grade plastic container.

217. CMP-PCT does not specifically disclose the use of 900 mg /100 ml (0.9%) sodium chloride (saline) in its solutions. However, CMP-PCT does teach that its diluted solutions should contain dextrose, which is a common tonicity agent. (Ex-1007 at 4:28-30.) As I explained previously, another common tonicity agent is saline. (See §VI.B. *supra*, citing Ex-1013 at 100; Ex-1014 at 637; Ex-1010 at 540; Ex-1026 at 309.) 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 and Terlevich to ensure the RTU solution has the proper tonicity.

218. Furthermore, as explained previously, the exact solution disclosed by CMP-PCT was approved for use by the FDA in September 2019 (*see* §VII.B.3, *supra*), and the FDA Drug Label for the CMP-PCT solution requires the diluted solution to have 0.9% NaCl:

“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.)

A POSITA would seek to comply with the FDA requirements 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 and Terlevich.

219. 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 is readily capable of producing CMP's solutions with 0.9% NaCl. (§VI.B, *supra*, citing Exs. 1008, 1010, 1013-14, 1026-27.)

220. For at least the above reasons, a POSITA would have been motivated to combine the teachings of the CMP Art and Terlevich to provide a RTU potassium phosphate solution in a RTU container having about (a) 583 mg/100 ml or 4.28 mmol/100 ml of KMP, (b) 1000 mg/100 ml or 5.74 mmol/100 ml of KDP, and (c) 0.9% NaCl (900 mg/100 ml) with a reasonable expectation of success.

221. Finally, as explained above, CMP-PCT teaches to use ultra-low levels of aluminum (≤ 1 ppm), with its solutions realizing 0.2-0.3 ppm Al after an extended period in a plastic container. (Ex-1007 at 20:1-7.) As I explain below, these CMP-PCT teachings alone render obvious the ≤ 50 mcg/L Al requirement of the '661 patent's claims.

222. Nonetheless, a POSITA would have been motivated to include as little as aluminum as possible in the RTU solutions taught by the CMP Art and Terlevich. As I explained in §VI.C, it was well-known that aluminum is toxic and also causes precipitation of particles in parenteral solutions. (Ex-1007 at 1:27-13; 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.)

Accordingly, a POSITA would have been motivated to use less than 50 ppb Al, preferably 25 ppb Al or less, in potassium phosphate buffer solutions, such as those taught by CMP-PCT.

223. As I also explained previously in §VI.C, Ogawa 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.”).)

224. As I also explained previously, 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.”).)

225. 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 (i.e., to use < 50 ppb Al, preferably 25 ppb Al or less) to the RTU solutions taught by the CMP Art and Terlevich to ensure that the CMP-PCT solutions avoided 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-1007 at 20:1-7.)

226. A POSITA also would have had a reasonable expectation of success in applying Ogawa’s teachings. CMP-PCT already recognizes that glasses should be avoided, and teaches to use plastic containers to avoid aluminum leaching over time. (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 637-638, Table 1 (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 potassium phosphate 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 RTU solutions taught by the CMP Art and Terlevich.

3. The Challenged Claims

[Claim 1, 1.0] A sterile ready-to-use aqueous potassium solution, comprising potassium phosphates and sodium chloride, ...

227. The CMP Art in view of Terlevich teaches this limitation.

228. 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.)

229. Further, as explained in §X.B.2, *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.B.2, 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.)

230. 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.”

231. Further, as explained in §§VI.B and X.B.2, the use of saline as a tonicity agent in 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.)

232. Thus, the CMP Art in view of Terlevich teaches this limitation.

[1.1] wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorous and,

233. CMP-PCT in view of Terlevich teaches this limitation.

234. CMP-PCT teaches undiluted solutions having 300 mg/ml and 175 mg/ml of KDP and KMP, respectively. (Ex-1007 at 2:29-32.) As I explained in §X.B.2, above, it was obvious in view of Terlevich to produce the CMP-PCT solutions as RTU solutions with 30-times lower KMP and KDP concentrations, resulting in a RTU solution having 4.28 mmol/100 ml KMP and 5.74 mmol/100 ml KDP, or a total phosphate concentration of about 10 mmol/100 ml. A phosphorous concentration of 10 mmol/ 100 ml lies within, and thus discloses, the claimed range.

235. Accordingly, CMP-PCT in view of Terlevich teaches this limitation.

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

236. CMP-PCT teaches this limitation, optionally in view of Ogawa.

237. CMP-PCT teaches that to use ultra-low levels of aluminum (≤ 1 ppm) and its example solutions even contained as little as 0.2 ppm Al (200 ppb Al) of :

“A tenth aspect of the first or second embodiment is directed to *a plastic vial* comprising the composition of the first or second embodiment

having an aluminum content of ***not more than***...about 1 ppm after storage ***at 4-8°C*** for 3-months, 6-months, 12-months, 18-months, 24-months, 36-months, or longer (e.g, 48-months).” (Ex-1007 at 4:4-9.)

“An eleventh aspect of the first or second embodiment is directed to ***a plastic vial*** comprising the composition of the first or second embodiment having an aluminum content of not more than...about 1 ppm after ***storage at room temperature*** for 3 -months, 6-months, 12-months, 18-months, 24-months, 36-months, or longer (e.g, 48-months).” (*Id.* at 4:10-15.)

“ *The reduction in aluminum content with storage at 4-8°C is particularly advantageous because it provides for a composition [sic] that can be administered to patients with renal insufficiency that does not exceed the recommended maximum daily aluminum dose of 4 to 5 mcg/kg/day....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 19:19-28.)

238. As I explained above in §X.B.2, these CMP-PCT teachings alone render obvious the ≤ 50 mcg/L Al requirement of the '661 patent's claims because the ≤ 50 mcg/L claim requirement appears arbitrary given the '661 patent allows for up to 4.2 ppm of Al (4200 mcg/L) in its solution preparation materials, which is indistinct from the “not more than 5 ppm” requirement of CMP-PCT. (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).)

239. Ogawa shows that even 50 ppb aluminum (50 mcg/L), may problematically result in particulate generation in potassium buffer solutions (Ex-1010 at 544-45), i.e., a POSITA would not have expected any material difference in a potassium phosphate buffer solution having 50 ppb Al or 200 ppb Al (i.e., 50 mcg/L Al or 200 mcg/L Al)—both levels of aluminum would tend to cause generation of insoluble particulate particles. (*See* VI.C, *supra*.)

240. Thus, a POSITA would have found this limitation obvious based on CMP-PCT alone.

241. This limitation (1.2) is also taught by CMP-PCT in view of Ogawa. As explained in §X.B.2, based on Ogawa, a POSITA would have been motivated to use <50 ppb Al (<50 mcg/L), and preferably 25 ppb Al or less, in parenteral phosphate buffer solutions, such as those containing KMP and KDP, like CMP-PCT, to avoid particle formation, and a POSITA would have had a reasonable expectation of successfully preparing such solutions.

242. Thus, CMP-PCT in view of Ogawa also teaches this limitation.

[1.3] wherein the solution has a pH of between 6.2 and 6.8

243. CMP-PCT teaches this limitation.

244. 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 and Terlevich 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. Indeed, the pH of 0.9% NaCl (standard saline) is 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.

245. Thus, the CMP Art view of Terlevich, optionally in view of Ogawa, teach all limitations of claim 1, and render obvious claim 1.

[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.

246. CMP-PCT in view of Terlevich teaches this limitation.

247. As I explained in §X.B.2 and claim 1, a POSITA would have found it obvious based on the teachings of CMP-PCT and Terlevich to produce a RTU solution having 4.28 mmol/100 ml KMP and 5.74 mmol/100 ml KDP. The molar ratio of KDP:KMP in this solution is 1.34, which teaches a ratio of 1.3 when considering one significant figure.

248. Further, even if two significant figures are considered, a ratio of 1.34 is indistinct from a ratio of 1.30 to a POSITA as the solution would be expected to have materially the same properties with a 1.30 or 1.34 molar ratio of KDP to KMP. The total amount of phosphate remains at 10 mmol/10 ml at a molar ratio of 1.30 or

1.34, and particulate generation would not be expected at a molar ratio of either 1.30 or 1.34 as CMP expressly shows.

249. Thus, claim 2 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[Claim 3] The solution of claim 2, wherein the [KDP] is present in the solution an amount of between about 112 mg/100 ml and about 1,120 mg/100 ml and wherein the [KMP] is present in the solution in an amount of between about 118 mg/100 ml and about 1,180 mg/100 ml.

250. CMP-PCT in view of Terlevich teaches this limitation.

251. As I explained in §X.B.2 and claim 1, it was obvious to a POSITA based on the teachings of CMP-PCT and Terlevich to produce a RTU solution having 583 mg/100 ml KMP and 1000 mg/100 ml KDP. These amounts of KMP and KDP lie within the claimed ranges.

252. Thus, claim 3 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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.

253. CMP-PCT in view of Terlevich teaches this limitation.

254. CMP-PCT teaches that its undiluted solutions include “about 4.7 mEq/mL” or 470 mEq per 100 mL of potassium. (Ex-1007 at 17:1-8.) As explained in §X.B.2 and claim 1, it was obvious to a POSITA based on the teachings of CMP-PCT and Terlevich to produce a RTU solution diluted by a factor of 30. Thus, CMP-

PCT in view of Terlevich teaches a solution having a potassium content of 15.7 mEq (470/30=15.7) per 100 ml of solution, i.e., “no more than 22 mEq/100 mL.”

255. Thus, claim 4 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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.

256. The CMP Art in view of Terlevich teaches this limitation.

257. As I explained in in §X.B.2 and claim 1, it was conventional and obvious to use 0.9% (900 mg/100 ml) of sodium chloride, commonly known as normal saline, in intravenously administered phosphate solutions. Moreover, CMP-FDA requires 0.9% saline in diluted CMP solutions. (Ex-1008 at 2; Ex-1027 at 4.)

258. Thus, claim 5 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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 25 micrometer size, respectively.

259. CMP-PCT in view of Terlevich teaches this limitation.

260. CMP-PCT teaches that its solutions contain no particles visible after extended periods of storage in plastic vials at either 4-8°C or 25°C 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 teaches the use of standardized tests to evaluate the presence of particles. (Ex-1007 at 11:30-32 (“The compositions were evaluated initially for Appearance (APP) and Visible Particles (VP) according to the Universal Test and USP 41 <790> Visible”).).)

261. Further, as I explained in §X.B.2, preparing RTU solutions based on the teachings of CMP-PCT and Terlevich would not have been expected to alter the particle content of the CMP-PCT solutions.

262. 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. Terlevich’s semi-rigid, polyethylene RTU containers had been commercially used for at least 13 years, i.e., were a known, conventional RTU container option and

stably maintained RTU potassium phosphate solutions.⁶

263. Terlevich's RTU polyethylene containers also would not have contained leachable aluminum

264. Further, large volume parenteral (LVP) containers were well-known to prevent moisture and oxygen penetration, thereby preventing solution degradation and particulate generation:

“LVP refer to sterile diluents, electrolytes, irrigating fluids, blood derivatives, nutritional preparations and premixed injectable drugs administered in quantities of over 100 mL. LVP are packaged in semi-rigid plastic containers, *flexible minibags* and, to a lesser extent, glass containers....*The sterile formulation of LVP necessitates the use of containers with good barrier properties...*” (Ex-1013 at 317.)

265. Based on the foregoing, a POSITA would have reasonably expected the RTU solutions taught by CMP-PCT and Terlevich, when stored in a suitable RTU container, such as the “semi-rigid cylindrical polyethylene container” of Terlevich, to achieve the claim requirements of “after autoclaving and storage of at least 3 months at 25° C and 40% relative humidity, a total liquid particle count of no more

⁶ The Terlevich article published in 2003 and the Wadsworth article published in 2016, i.e., thirteen years apart, and both reference the Phosphate Polyfusor® of Fresenius.

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 (steam sterilization) of parenteral packaging was conventional:

“Flexible medical containers are known in the art for the containment and delivery of medical fluids. Such containers serve for accommodating blood *or for sterile storage of infusion solutions* and diagnostic media *for parenteral administration*. For these purposes the containers must be sterile and *sterility is achieved by heating to at least 100°C or more in an autoclave*. Sterility must be maintained during storage and administration of the medical fluids such that environmental conditions such as atmospheric oxidation will not jeopardize the integrity of the medical fluids.” (Ex-1033 at 1:17-26.)

“A further important object of the present invention is to provide a film material with high heat resistance capable of maintain its shape when subjected to *heat sterilization with pressurized steam (autoclavation) of at least 121°C for at least 15 minutes*, while maintaining the aforementioned characteristics.” (Ex-1035 at 7:10-15.)

CMP-PCT also teaches to autoclave the containers used with its potassium phosphate solutions:

“An eighteenth aspect of the first or second embodiment is directed to a process for preparing the composition of the first or second embodiment, which comprises: (a) dissolving an amount of potassium dibasic phosphate in a vessel containing a first amount of water that represents about 25% of the total amount of water; (b) adding a second

amount of water that represents about 60% of the total amount of water to the composition of step (a); (c) dissolving an amount of potassium monobasic phosphate in the composition of step (b); (d) adding a third amount of water to the composition of step (c) to provide about 175 mg/mL potassium monobasic phosphate and about 300 mg/mL of potassium dibasic phosphate; (e) filtering the composition of step (d) through a membrane having a plurality of pores each with a pore diameter of about 0.2 μ m; (f) dispensing a volume of the composition of step (e) into a vial; (g) sealing the vial of step (f); and ***(h) heating the vial of step (g) at a temperature of about 121 °C for about 15 minutes to about 30 minutes.***” (Ex-1007 at 5:25-6:4.)

“Some vials (aseptic samples) were set aside for further analysis, ***while other vials were terminally sterilized (TS samples).*** Each vial contains about 175 mg/mL KMP, about 300 mg/mL KDP, and (c) a sufficient amount of a water vehicle to provide total amount of phosphate of about 3 mmol/mL.” (Ex-1007 at 18:24-27.)

266. Thus, claim 6 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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.

267. CMP-PCT in view of Terlevich teaches claims 7 and 8.

268. As I explained above relative to claim 6, a POSITA would have

expected the diluted CMP-PCT solutions to be stable when packaged in an appropriate pharmaceutical grade RTU containers, such as the Terlevich container.

269. 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 “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,” over time, a POSITA would have reasonably expected the phosphorous and potassium concentrations to be stable after many months of storage in a conventional RTU container.

270. Potassium phosphate solutions were known to be highly stable. For instance, in 2017 Perks tested the stability of potassium phosphate solutions in standard PVC IV bags:

“Objective: To evaluate the physical compatibility and chemical stability of 30 and 150 mmol/L solutions of phosphate, prepared from sodium phosphate injection, in 5% dextrose in water (D5W) and in 0.9% sodium chloride (normal saline [NS]) and stored in polyvinyl chloride (PVC) bags at 23°C or 4°C over 63 days.” (Ex-1030 at 7.)

Despite being tested in PVC, which had known water permeability and other issues, “the concentrations of both sodium and phosphate *remained unchanged*” when corrected for water loss:

“CONCLUSION

In this study, sodium and phosphate concentrations in IV admixtures prepared and stored in PVC containers increased over the 63-day study period as a result of water loss from the PVC bags. *When measurements were corrected for water loss, the concentrations of both sodium and phosphate remained unchanged*, and the 95% CI of the degradation rate encompassed a loss rate of 0%/day.” (*Id.* at 12.)

271. Accordingly, a POSITA would have reasonably expected CMP-PCT solutions stored in an appropriate RTU container to achieve the requirements of claims 7 and 8, i.e., “a change in phosphorus of no more than 1% absolute” and “a change in potassium of no more than 2% absolute” “after autoclaving and storage of at least 3 months at 25° C and 40% relative humidity.”

272. Thus, claims 7 and 8 are obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

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

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

274. Terlevich teaches that its RTU solutions are stored in a “semi-rigid cylindrical polyethylene container.” (Ex-1009 at 1326.) 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 “semi-rigid,” i.e., have some flexibility, otherwise the author would have not used the word “semi-” with the word “rigid.”

“High-density polyethylene (HDPE): The polymer is based on a simple repeating carbon/hydrogen molecule that branches out during polymerization to form a polymer with a high degree of regularity.... structures. Polyethylene (PE) is recognized as having a high degree of crystallinity....As a result of their relatively high degree of crystallinity as compared with lower-density PEs, HDPEs have greater tensile strength and stiffness and have a higher melting point than the low-density polyethylene (LDPE) resins....Both HDPE and LDPE are used to form containers by blow-fill-seal technology, primarily for ophthalmic and nasal/respiratory drugs, ***but also have been used for both SVP and LVP products.***”

“LVP refer to sterile diluents, electrolytes, irrigating fluids, blood derivatives, nutritional preparations and premixed injectable drugs administered in quantities of over 100 mL. LVP are packaged in ***semi-rigid plastic containers***, flexible minibags and, to a lesser extent, glass containers....***The sterile formulation of LVP necessitates the use of containers with good barrier properties*** and sizes of semi-rigid plastic IV containers range from 250 mL for biologicals and nutritionals up to

4 L for standard diluents (such as sodium chloride and dextrose).” (Ex-1013 at 317.)

275. Further, as I 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 and Terlevich.

276. Thus, CMP-PCT in view of Terlevich discloses this 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,

277. For the same reasons I provided above relative to limitations 1.0 and 1.2, the CMP Art in view of Terlevich, optionally in view of Ogawa, teaches this limitation.

[11.2] (b) between about 1.5 mmol 100 ml and 15 mmol/100 ml phosphorus, and,

278. For the same reasons I provided above relative to limitation 1.1, CMP-PCT in view of Terlevich teaches this limitation.

[11.3] (c) no more than about 22 mEq/100 mL potassium.

279. For the same reasons I provided above relative to claim 4, CMP-PCT in view of Terlevich teaches this limitation.

280. Thus, the CMP Art in view of Terlevich, optionally in view of Ogawa, teaches all limitation of, and renders obvious, claim 11.

[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.

281. For the same reasons I provided above relative to claims 2-3, CMP-PCT in view of Terlevich teaches this limitation.

282. Thus, claim 12 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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.

283. For the same reasons I provided above relative to claim 5, CMP-PCT in view of Terlevich teaches this limitation.

284. Thus, claim 13 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container

285. The CMP Art in view of Terlevich disclose these limitations.

286. CMP-PCT teaches to intravenously administer its inventive compositions to patients in need of phosphorus replacement therapy. (Ex-1007 at

4:23-5:9.)

287. Further, as shown in claim 1, limitation 1.0, the CMP Art in view of Terlevich discloses 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.

288. Finally, 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.

289. Thus, the CMP Art in view of Terlevich teaches this 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;

290. CMP-FDA teaches this limitation.

291. Specifically, §2.3, Table 2 of FDA-2019 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-1008 at 4; Ex-1027 at 6.)

292. Thus, CMP-FDA teaches this limitation.

[17.2] wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus,

293. For the same reasons I provided above relative to limitation 1.1, CMP-PCT in view of Terlevich teaches this limitation.

[17.3] no more than about 22 mEq/100 mL potassium, and

294. For the same reasons I provided above relative to claim 4, CMP-PCT in view of Terlevich teaches this limitation.

[17.4] less than 50 mcg/L aluminum.

295. For the same reasons I provided above relative to limitation 1.2, CMP-PCT, optionally in view of Ogawa, teaches this limitation.

296. Thus, the CMP Art in view of Terlevich, optionally with Ogawa, teaches all limitations of claim 17, and render obvious claim 17.

[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.

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

298. CMP-FDA teaches claim 18. 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.)

299. Thus, claim 18 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

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

300. 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.)

301. Thus, claim 19 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

[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.

302. CMP-PCT teaches this limitation.

303. As I 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 and Terlevich to remain stable when stored for 3-months or more in a suitable pharmaceutical grade RTU container, such as Terlevich’s RTU container.

304. CMP-PCT teaches that its solutions can be administered even after 24-months of storage at 25°C and 60% relative humidity (RH). (Ex-1007 at 3:18-21, 4:23-5:9.) A POSITA would reasonably expect that, because CMP’s solution may be administered after 24-months of storage at 25°C and 60% RH, the CMP diluted solutions would also be suited for administration after 3-months of storage at 25°C and 40% RH because it is highly unlikely that the lower potassium phosphate

concentration or the lower relative humidity would meaningfully change the outcome after storage for 3-months or even 24-months. This is at least because, as I explained above relative to claims 6-8, the Terlevich semi-rigid polyethylene containers would have prevented unwanted permeation of water or oxygen.

305. Thus, claim 20 is obvious over the CMP Art in view of Terlevich, optionally in view of Ogawa.

C. Ground 3: The Ground 2 Art in view of Nevakar teaches claims 9-20

1. Summary of Ground 3

306. Ground 3 relies on the Ground 2 art plus Nevakar. The Ground 2 art teaches most claim limitations except those relating to multiple layer flexible containers and applying a secondary metallized overwrap to such containers. Nonetheless, such containers and overwraps were conventional as shown by Nevakar. As I also show below, it was obvious to package the RTU solutions taught by the Ground 2 art using the packaging teachings of Nevakar.

2. Reasons to Combine the Ground 2 Art with Nevakar

307. A POSITA would have been motivated and found it obvious to combine the teachings of the Ground 2 art and Nevakar for the reasons provided below.

308. As I explained in §VI.D.4, the '661 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 '661 patent simply employed off-the-shelf products to store its solutions. Further, as explained above relative to Ground 2, CMP-PCT teaches the use of glass or plastic vials while Terlevich teaches the use of semi-rigid polymeric containers. Neither reference specifically teaches the use of multilayer, flexible containers for use with ready-to-use solutions. Nonetheless, such containers were conventional.

309. Specifically, Nevakar (Ex-1011) teaches flexible bags suited for use with ready-to-use solutions and secondary metallized overwraps:

“Therefore, in yet another aspect of the inventive subject matter, the inventors also contemplate a pharmaceutical product, *a polymeric container that includes the antioxidant-free and storage stable ready-to-administer composition* containing an oxygen-sensitive drug, such as the epinephrine composition presented herein, *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 polyvinyl chloride, **polyethylene, polypropylene**, polyethylene terephthalate, various co-polymers such as ethylene-propylene copolymers, ethylene vinyl acetate, copolyester ether polymers, etc. *Such polymeric containers may preferably, but not necessarily have a reduced oxygen permeability (e.g., where no overwrap is used). These*

containers or bags may then preferably packaged into an overwrap (or other secondary package) that has one or more additional properties that help maintain stability. ... 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. For example, 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).” (Ex-1011 at 0037.)

310. A POSITA would have been motivated to use the polymeric containers and secondary metallized overwraps described by Nevakar with the ready-to-use solutions taught by the Ground 2 art (The CMP Art, Terlevich (Exs. 1007-09, 1027)). Nevakar describes that its containers are well-suited for use with ready-to-use solutions and assists in maintaining the stability of such solutions, and solution stability 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.

311. A POSITA would also have had reasonable expectation of using Nevakar’s containers with the ready-to-use solutions taught by the Ground 2 art

because it would have been simple to package the ready-to-use solutions of the Ground 2 art using the Nevakar containers. (Ex-1011 at 0035-36 (showing simplicity of filling containers with solution); 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 2 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. (See Ex-1011 at 0015, 0037; Ex-1013 at 309 (“Multilayer plastics” discussion) and 317-18 (LVP/minibag discussion), showing such LVP containers must have “strong barrier[s] to water vapor transmission” and “sterile formulation of LVP necessitates the use of containers with good barrier properties.”); Ex-1033 at 1:26-2:5 (describing conventional metallized overwraps).)

312. Accordingly, a POSITA would have found it obvious to use the Nevakar containers with the ready-to-use solution taught by the Ground 2 art.

3. The Challenged Claims

[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.

313. As I explained above in §X.C.2, it was obvious to a POSITA to combine the teachings of Nevakar with the Ground 2 art wherein the RTU solutions

taught by the Ground 2 art are packaged in the flexible RTU containers of Nevakar.

314. As I explained above for Ground 2, claim 9 includes one mandatory limitation and two optional limitations (volume and multilayer). Nonetheless, Nevakar teaches all claimed features.

315. Nevakar disclose the use of 100-1000 ml multiple-layer, flexible 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 with a volume of at least 100 ml, or at least 200 ml, or at least 300 ml, or at least 400 ml, or at least 500 ml, or at least 1,000 ml, wherein the polymeric bag may be manufactured from polyvinyl chloride, **polyethylene, polypropylene**, polyethylene terephthalate, various copolymers such as ethylene-propylene copolymers, ethylene vinyl acetate, copolyester ether polymers, etc.... 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.”* (Ex-1011 at 0037.)

316. A POSITA would recognize that many of the polymers described by Nevakar above are polyolefins. (Ex-1034 at 6:54-64 (“It is preferred that film is

made of at least two different polymer layers of which at least the inner sealant layer is *based on polyolefins, such as polyethylenes or polypropylenes of various qualities which are chemically inert to the stored fluids, autoclavable, weldable and possible to recycle*. The terms ‘polyethylenes’ and ‘polypropylenes’ are intended to include both homopolymers and copolymers having such mentioned characteristics unless otherwise is specified. Preferably, the sealant layer is based on polypropylene including its copolymers with ethylene (propylene ethylene copolymer) and/or its mixtures with polyethylene.”.)

317. Thus, claim 9 is obvious over the Ground 2 art further in view of Nevakar.

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

318. Nevakar teaches this limitation.

319. Nevakar discloses 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.)

“For example, the polymeric container may be configured as a flexible bag with a volume of at least 100 ml [and]... 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. *For example, 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.)

320. A POSITA would have known that placing a flexible polyolefin container in a secondary metallized overwrap further protects the solution from premature degradation as well as prevents or substantially restricts unwanted evaporation. Secondary metallized overwraps were well-known in the art:

“In order to maintain the integrity of the medical fluids both during the sterilization process and storage, the medical bag is packaged in a first packaging material or overwrap having sufficient gas permeability and heat resistance able to withstand heat on autoclaving, and a second packaging material or overwrap which has a high oxygen impermeability. ***This double packaging results in good shelf life***, such as disclosed, for example in U.S. Pat. No. 4,548,605. Other efforts to maintain the integrity of medical fluids during and subsequent to sterilization included the use of multi-layer packaging, such as disclosed in U.S. Pat. No. 4,660,721.” (Ex-1033 at 1:27-37.)

“Certain medical fluids are not only oxygen-sensitive, but also light-sensitive. To prevent TV rays reaching the ophthalmic solution in a vessel, U.S. Pat. No. 4,150,744 discloses the use of ***a laminate comprising nylon, aluminum foil and polypropylene with which the vessel is overwrapped***. Such laminates, containing a metal foil widely

used for pouches and bags containing intravenous solutions.” (*Id.* at 1:41-47.)

321. “Applicants have now discovered that, in addition to providing a medical container having the required properties to allow autoclave sterilization, *may be packaged in an overwrap which is substantially resistant to UV rays penetration, yet allow viewing the content of the medical bottle and its identifying inscription.*” (*Id.* at 1:65-2:3.) Thus, the Ground 2 art in view of Nevakar teaches and renders obvious claim 10.

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

322. For the reasons I provided above relative to Ground 2, limitation 11.0, CMP-PCT in view of Terlevich teaches a “sterile ready-to-use premixed pharmaceutical product.”

323. For the reasons I provided above relative to claim 9, Nevakar teaches “a flexible polymeric container.”

324. Further, as I explained above relative to §X.C.2, a POSITA would have been motivated to apply Nevakar’s flexible polymeric container teachings with the Ground 2 art, and with a reasonable expectation of success.

325. Thus, the Ground 2 art in view of Nevakar teaches this 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,

326. For the same reasons I provided above relative to Ground 2, limitation [11.1], the Ground 2 art teaches this limitation.

[11.2] (b) between about 1.5 mmol 100 ml and 15 mmol/100 ml phosphorus, and,

327. For the same reasons I provided above relative to Ground 2, limitation [11.2], the Ground 2 art teaches this limitation.

[11.3] (c) no more than about 22 mEq/100 mL potassium.

328. For the same reasons I provided above relative to Ground 2, limitation 11.4, the Ground 2 art teaches this limitation.

329. Thus, the Ground 2 art in view of Nevakar teaches all limitation of, and renders obvious, claim 11.

[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.

330. For the same reasons I provided above relative to Ground 2, claim 12, the Ground 2 art teaches this limitation.

331. Thus, claim 12 is obvious over the Ground 2 art in view of Nevakar.

[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.

332. For the same reasons I provided above relative to Ground 2, claim 13, the Ground 2 art teaches this limitation.

333. Thus, claim 13 is obvious over the Ground 2 art in view of Nevakar.

[Claim 14] The pharmaceutical product of claim 11, wherein the premixed pharmaceutical product in the flexible polymeric container has a volume of between 100 mL and 1,000 mL.

[Claim 15] The pharmaceutical product of claim 14, wherein the flexible polyolefin container is a flexible multilayer bag.

334. Nevakar teaches the limitations of claims 14-15 (100-1000 ml volume; flexible multilayer bag) for the same reasons provide above relative to claim 9.

335. Thus, claims 14-15 are obvious over the Ground 2 art in view of Nevakar.

[Claim 16] The pharmaceutical product of claim 11, wherein the flexible polymeric container is enclosed in a secondary metallized overwrap.

336. Nevakar teaches the limitation of claim 16 for the same reasons provide above relative to claim 10.

337. Thus, claim 16 is obvious over the Ground 2 art in view of Nevakar.

[Claim 17, 17.0] A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising:

338. For the same reasons I provided above relative to Ground 2, claim 17, limitation 17.0, the Ground 2 art teaches this limitation.

[17.1.A] administering, without prior dilution, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution from a flexible container

339. For the same reasons I provided above relative to Ground 2, claim 17, limitation 17.1, the Ground 2 art teaches “administering, without prior dilution, a sterile, and ready-to-use solution comprising potassium phosphates and sodium chloride solution.”

340. For the same reasons I provided above relative to claim 9, Nevakar teaches flexible containers and a POSITA would have been motivated to use Nevakar’s flexible containers with the RTU solutions taught by the Ground 2 art and with a reasonable expectation of success.

341. Thus, the Ground 2 art in view of Nevakar teaches this 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;

342. For the same reasons I provided above relative to Ground 2, claim 17, limitation 17.1.B, the Ground 2 art teaches this limitation.

[17.2] wherein the solution comprises between 1.5 mmol/100 mL and 15 mmol/100 ml phosphorus,

343. For the same reasons I provided above relative to Ground 2, claim 17, limitation 17.2, the Ground 2 art teaches this limitation.

[17.3] no more than about 22 mEq/100 mL potassium, and

344. For the same reasons I provided above relative to Ground 2, claim 17,

limitation 17.3, the Ground 2 art teaches this limitation.

[17.4] less than 50 mcg/L aluminum.

345. For the same reasons I provided above relative to Ground 2, claim 17, limitation 17.4, the Ground 2 art teaches this limitation.

346. Thus, the Ground 2 art in view of Nevakar teaches all limitation of, and renders obvious, claim 17.

[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.

347. The Ground 2 art teaches this limitation for the reasons provided in Ground 2, claim 18.

348. Thus, claim 18 is obvious over the Ground 2 art in view of Nevakar.

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

349. The Ground 2 art teaches this limitation for the reasons provided in Ground 2, claim 19.

350. Thus, claim 19 is obvious over the Ground 2 art in view of Nevakar.

[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.

351. As I explained above in Ground 2, claim 20, CMP-PCT teaches that its solutions can be administered even after 24-months of storage at 25°C and 60% relative humidity (RH), and a POSITA would reasonably expect that, because CMP's solution may be administered after 24-months of storage at 25°C and 60%

RH, the CMP diluted solutions would also be suited for administration after 3-months of storage at 25°C and 40% RH because it is highly unlikely that the lower potassium phosphate concentration or the lower relative humidity would meaningfully change the outcome after storage for 3-months or even 24-months. This is at least because, as I explained above relative to claims 6-8, the Terlevich semi-rigid polyethylene containers would have prevented unwanted permeation of water or oxygen.

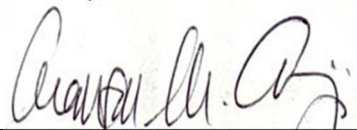
352. A POSITA also would have reasonably expected to achieve this limitation when using the flexible polymeric containers of Nevakar with the RTU potassium phosphate solutions taught by the Ground 2 art. As I explained above in §X.C.2, the Nevakar flexible polymeric containers reduce permeability and, therefore, would reasonably be expected to prevent or substantially restrict evaporation because Nevakar discloses multilayered and use moisture impermeable polymers containers known to prevent evaporation and oxygen penetration. Accordingly, a POSITA would have expected the RTU potassium phosphate solutions taught by the Ground 2 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.

353. Thus, claim 20 is obvious over the Ground 2 art in view of Nevakar.

XI. CONCLUSION

354. This declaration and my opinions herein are made to the best of my knowledge and understanding, and based on the material available to me, at the time of signing this declaration. I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 or Title 18 of the United States Code.

Date: April 11, 2025

A handwritten signature in dark ink, appearing to read "Mansoor M. Amiji", is written over a horizontal line.

Mansoor M. Amiji, Ph.D.

APPENDIX A

Drugs@FDA: FDA-Approved Drugs

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Search Results for "Potassium Phosphates"

Products listed on this page may not be equivalent to one another. (http://www.fda.gov/drugs/informationondrugs/ucm075234.htm#searches_about)

POTASSIUM PHOSPHATES

- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212121>) | NDA #212121 | SOLUTION;INTRAVENOUS | Discontinued | CMP DEV LLC
- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212832>) | NDA #212832 | SOLUTION;INTRAVENOUS | Prescription | FRESENIUS KABI USA
- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=216274>) | ANDA #216274 | SOLUTION;INTRAVENOUS | Prescription | AM REGENT
- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=216344>) | ANDA #216344 | SOLUTION;INTRAVENOUS | Prescription | AMNEAL
- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217726>) | ANDA #217726 | SOLUTION;INTRAVENOUS | Prescription | SOMERSET THERAPS LLC
- **POTASSIUM PHOSPHATES (POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC)** (</scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217892>) | ANDA #217892 | SOLUTION;INTRAVENOUS | Prescription | CIPLA

POTASSIUM PHOSPHATES IN 0.9% SODIUM CHLORIDE

Drugs@FDA: FDA-Approved Drugs

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New Drug Application (NDA): 212121

Company: CMP DEV LLC

✉ [EMAIL \(MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTP://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS%26VARAPPLNO=212121\)](mailto:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTP://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS%26VARAPPLNO=212121)

Products on NDA 212121



CSV

Excel

Print

Drug Name	Active Ingredients	Strength	Dosage Form/ Route	Marketing Status	TE Code	RLD	
POTASSIUM PHOSPHATES	POTASSIUM PHOSPHATE, DIBASIC; POTASSIUM PHOSPHATE, MONOBASIC	4.5GM/15ML (300MG/ML);2.65GM/15ML (175MG/ML)	SOLUTION;INTRAVENOUS	Discontinued	None	Yes	N

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 212121



Labels for NDA 212121



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **POTASSIUM PHOSPHATES INJECTION** safely and effectively. See full prescribing information for **POTASSIUM PHOSPHATES INJECTION**.

POTASSIUM PHOSPHATES injection, for intravenous use

Initial U.S. Approval: 1983

INDICATIONS AND USAGE

POTASSIUM PHOSPHATES INJECTION is a phosphorus replacement product indicated as a source of phosphorus:

- in intravenous fluids to correct hypophosphatemia in adults and pediatric patients 12 years of age and older when oral or enteral replacement is not possible, insufficient or contraindicated. (1.1)
- for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated. (1.2)
 - **Limitations of Use:** Safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risk of aluminum toxicity. (1.2, 5.5, 8.4)

DOSAGE AND ADMINISTRATION

- Administer intravenously only after dilution or admixing in a larger volume of fluid. (2.1)
- POTASSIUM PHOSPHATES INJECTION provides phosphorus 3 mmol/mL (potassium 4.7 mEq/mL). (2.2, 2.4)
- Monitor serum phosphorus, potassium, calcium, and magnesium concentrations. (2.2, 2.4)
- See full prescribing information for instructions on preparation and administration. (2.1, 2.3)

Recommended Dosage for Correction of Hypophosphatemia in Intravenous Fluids:

- POTASSIUM PHOSPHATES INJECTION is only for administration to a patient with a serum potassium concentration less than 4 mEq/dL; otherwise, use an alternative source of phosphate. (2.1)
- The dosage is dependent upon the individual needs of the patient, and the contribution of phosphorus and potassium from other sources. (2.2)
- See full prescribing information for recommendations on initial or single dosing, repeated dosing, concentration and infusion rate. (2.1, 2.2)

Recommended Dosage for Administration in Parenteral Nutrition:

- Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. (2.4)
- See full prescribing information for recommendations for daily and maximum dosage. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

- hyperkalemia
- hyperphosphatemia (4)
- hypercalcemia or significant hypocalcemia (4)
- severe renal impairment (eGFR less than 30 mL/min/1.73m²) and end stage renal disease (4)

WARNINGS AND PRECAUTIONS

- **Serious Cardiac Adverse Reactions with Undiluted Bolus, or Rapid Intravenous Administration:** Administer only after dilution or admixing; do not exceed the recommended infusion rate. Continuous electrocardiographic (ECG) monitoring may be needed during infusion. (5.1)
- **Pulmonary Embolism due to Pulmonary Vascular Precipitates:** If signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation. (5.2)
- **Hyperkalemia:** Increased risk in patients with renal impairment, severe adrenal insufficiency, or treated with drugs that increase potassium. Patients with cardiac disease may be more susceptible. Do not exceed the maximum daily amount of potassium or the recommended infusion rate. Continuous ECG monitoring may be needed during infusion. (5.3, 7.1)
- **Hyperphosphatemia and Hypocalcemia:** Monitor serum phosphorus and calcium concentrations during and following infusion. (5.4)
- **Aluminum Toxicity:** Increased risk in patients with renal impairment, including preterm infants. (5.5, 8.4)
- **Hypomagnesemia:** Reported in patients with hypercalcemia and diabetic ketoacidosis. Monitor serum magnesium concentrations during treatment. (5.6)
- **Vein Damage and Thrombosis:** Infuse concentrated or hypertonic solutions through a central catheter. (2.1, 2.3, 5.7)

ADVERSE REACTIONS

Adverse reactions are hyperkalemia, hyperphosphatemia, hypocalcemia and hypomagnesemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact CMP Pharma at 1-844-321-1443 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use of Other Medications that Increase Potassium: Avoid use in patients receiving such products. If use cannot be avoided, closely monitor serum potassium concentrations. (5.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.2 For Parenteral Nutrition

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- 2.4 Dosage for Administration in Parenteral Nutrition

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4 CONTRAINDICATIONS

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- 5.3 Hyperkalemia
- 5.4 Hyperphosphatemia and Hypocalcemia
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 In Intravenous Fluids to Correct Hypophosphatemia

POTASSIUM PHOSPHATES INJECTION is indicated as a source of phosphorus in intravenous fluids to correct hypophosphatemia in adults and pediatric patients 12 years of age and older when oral or enteral replacement is not possible, insufficient or contraindicated.

1.2 For Parenteral Nutrition

POTASSIUM PHOSPHATES INJECTION is indicated as a source of phosphorus for parenteral nutrition in adults weighing at least 45 kg and pediatric patients 12 years of age and older weighing at least 40 kg when oral or enteral nutrition is not possible, insufficient or contraindicated.

Limitations of Use

Safety has not been established for parenteral nutrition in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risk of aluminum toxicity [see *Warnings and Precautions* (5.5), *Use in Specific Population* (8.4)].

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Administration in Intravenous Fluids to Correct Hypophosphatemia

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).
- The concentration of the diluted solution should take into consideration the amounts of phosphorus and potassium to be administered and is dependent upon whether administration will be through a peripheral or central venous catheter. The recommended maximum concentration is:
 - phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL) for peripheral administration
 - phosphorus 18 mmol/100 mL (potassium 28.2 mEq/100mL) for central administration
- Visually inspect the solution for particulate matter and discoloration before and after dilution and prior to administration. Do not administer unless solution is clear, and seal on the vial is intact.

Administration

- Check serum potassium and calcium concentrations prior to administration. Normalize the calcium before administering POTASSIUM PHOSPHATES INJECTION [see *Contraindications* (4), *Warnings and Precautions* (5.3,5.4)].
- POTASSIUM PHOSPHATES INJECTION is only for administration to a patient with a serum potassium concentration less than 4 mEq/dL [see *Warnings and Precautions* (5.3)]. If the potassium concentration is 4 mEq/dL or more, use an alternative source of phosphate.
- Do not infuse with calcium-containing intravenous fluids [see *Warnings and Precautions* (5.4)].
- The rate of administration may be dependent on the patient and the specific institution policy [see *Dosage and Administration* (2.2)].

Storage and Stability

- For single use only. Discard used vial, including any unused contents.
- After dilution, the solution is stable for 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature from 20°C to 25°C (68°F to 77°F).

2.2 Dosage for Administration in Intravenous Fluids to Correct Hypophosphatemia

POTASSIUM PHOSPHATES INJECTION provides phosphorus 3 mmol/mL (potassium 4.7 mEq/mL).

The dosage is dependent upon the individual needs of the patient, and the contribution of phosphorus and potassium from other sources.

Initial or Single Dose

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)].

In patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to <60 mL/min/1.73 m²), start at the low end of the dose range [see *Use in Specific Populations* (8.6)].

Monitor serum phosphorus, potassium, calcium and magnesium serum concentrations.

TABLE 1: Recommended Initial or Single Dose of POTASSIUM PHOSPHATES INJECTION in Intravenous Fluids to Correct Hypophosphatemia in Adults and Pediatric Patients 12 Years of Age and Older

Serum Phosphorus Concentration ^a	Phosphorus Dosage ^{b, c}	Corresponding Potassium Content
1.8 mg/dL to 2.4 mg/dL	0.16 mmol/kg to 0.31 mmol/kg	0.25 mEq/kg to 0.49 mEq/kg of potassium
1 mg/dL to 1.7 mg/dL	0.32 mmol/kg to 0.43 mmol/kg	0.5 mEq/kg to 0.68 mEq/kg of potassium
Less than 1 mg/dL	0.44 mmol/kg to 0.64 mmol/kg ^c	0.69 mEq/kg to 1 mEq/kg of potassium

^a Serum phosphorus reported using 2.5 mg/dL as the lower end of the reference range for healthy adults. Serum phosphorus concentrations may vary depending on the assay used and the laboratory reference range.

^b Weight is in terms of actual body weight. Limited information is available regarding dosing of patients significantly above ideal body weight; consider using an adjusted body weight for these patients.

^c up to a maximum of phosphorus 45 mmol (potassium 71 mEq) as a single dose.

Concentration and Intravenous Infusion Rate

- The concentration of the diluted solution and the infusion rate is dependent upon whether administration will be through a peripheral or central venous catheter.

Peripheral administration:

- The maximum recommended concentration is phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL).
- The maximum recommended infusion rate is approximately phosphorus 6.4 mmol/hour (potassium 10 mEq/hour)

Central administration:

- The maximum recommended concentration is phosphorus 18 mmol/100 mL (potassium 28.2 mEq/100 mL).
 - The maximum recommended infusion rate is approximately phosphorus 15 mmol/hour (potassium 23.5 mEq/hour).
- Continuous electrocardiographic (ECG) monitoring and infusion through a central venous catheter is recommended for infusion rates of potassium higher than 10 mEq/hour in adults and 0.5 mEq/kg/hour in pediatric patients 12 years of age and older.

Repeated Dosing

Additional dose(s) following the initial dose may be needed in some patients. Prior to administration of additional doses, assess the patient clinically and obtain serum phosphorus, calcium and potassium concentrations and adjust the dose accordingly.

2.3 Preparation and Administration in Parenteral Nutrition

- POTASSIUM PHOSPHATES INJECTION is for *intravenous infusion* into a peripheral or central vein *only after dilution and admixing*.
- POTASSIUM PHOSPHATES INJECTION is to be prepared only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). The key factor in the preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.

- Transfer the required amount of POTASSIUM PHOSPHATES INJECTION to the parenteral nutrition solution following the admixture of amino acids, dextrose, electrolytes solutions, and prior to lipids (if added).
- Because additives may be incompatible, evaluate all additions to the parenteral nutrition container for compatibility and stability of the resulting preparation.
- Calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in the formation of calcium-phosphate precipitates [see *Warnings and Precautions* (5.2)]. Calcium-phosphate stability in parenteral nutrition solutions is dependent upon the pH of the solution, temperature, and relative concentration of each ion. Discard if any precipitates are observed.
- Inspect the final parenteral solution containing POTASSIUM PHOSPHATES INJECTION to ensure that:
 - precipitates have not formed during mixing or addition of additives and inspect again before administration.
 - the emulsion has not separated, if lipids have been added. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.
- The final parenteral nutrition solution is for intravenous infusion into a peripheral or central vein. The choice of a peripheral or central venous route should depend on the osmolality of the final infusate. Solutions with osmolality of 900 mOsm/L or greater must be infused through a central catheter [see *Warnings and Precautions* (5.7)].

Storage and Stability

- For single use only. Discard used vial, including any unused contents.
- Use parenteral nutrition solution promptly after mixing. Any storage of the admixture should be under refrigeration from 2°C to 8°C (36°F to 46°F) and limited to a brief period of time, no longer than 24 hours. After removal from refrigeration, bring to room temperature and use promptly and complete the infusion within 24 hours. Discard any remaining admixture.
- Protect the parenteral nutrition solution from light during storage.

2.4 Dosage for Administration in Parenteral Nutrition

POTASSIUM PHOSPHATES INJECTION provides phosphorus 3 mmol/mL (potassium 4.7 mEq/mL).

The recommended and maximum daily dosage in parenteral nutrition is shown in Table 2. Individualize the dosage based upon the patient's clinical condition, nutritional requirements, and the contribution of oral or enteral phosphorus and potassium intake. The amount of phosphorus that can be added to parenteral nutrition may be limited by the amount of calcium that is also added to the solution.

TABLE 2: Recommended Daily Dosage of POTASSIUM PHOSPHATES INJECTION for Parenteral Nutrition

Patient Population	Generally Recommended Phosphorus Daily Dosage (Potassium Content)	Maximum Phosphorus Dosage (Potassium Content) Based Upon Aluminum Content ^a
Adults weighing at least 45 kg	20 mmol/day to 40 mmol/day ^b (potassium 31 mEq/day to 62.7 mEq/day)	45 mmol/day (potassium 71 mEq/day)
Pediatric patients 12 years of age and older weighing at least 40 kg		40 mmol/day (potassium 62.7 mEq/day)

^a see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.4)

^b In patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to <60 mL/min/1.73 m²), start at the low end of the dosage range.

Monitoring

Monitor serum phosphorus, potassium, calcium and magnesium concentrations and adjust the dosage accordingly.

3 DOSAGE FORMS AND STRENGTHS

POTASSIUM PHOSPHATES INJECTION, USP: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

POTASSIUM PHOSPHATES INJECTION is contraindicated in patients with:

- hyperkalemia [see *Warnings and Precautions* (5.3)]
- hyperphosphatemia [see *Warnings and Precautions* (5.4)]
- hypercalcemia or significant hypocalcemia [see *Warnings and Precautions* (5.4)]
- severe renal impairment (eGFR less than 30 mL/min/1.73m²) and end stage renal disease [see *Warnings and Precautions* (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiac Adverse Reactions with Undiluted, Bolus or Rapid Intravenous Administration

Intravenous administration of potassium phosphates to correct hypophosphatemia in single doses of phosphorus 50 mmol and greater and/or at rapid infusion rates (over 1 to 3 hours) in intravenous fluids has resulted in death, cardiac arrest, cardiac arrhythmia (including QT prolongation), hyperkalemia, hyperphosphatemia, and seizures [see *Overdosage* (10)]. In addition, inappropriate intravenous administration of undiluted or insufficiently diluted potassium phosphates as a rapid “IV push” has resulted in cardiac arrest, cardiac arrhythmias, hypotension, and death.

POTASSIUM PHOSPHATES INJECTION is for *intravenous infusion only after dilution or admixing*. The maximum initial or single dose of POTASSIUM PHOSPHATES INJECTION in intravenous fluids to correct hypophosphatemia is phosphorus 45 mmol (potassium 71 mEq). The recommended infusion rate is approximately phosphorus 6.4 mmol/hour (potassium 10 mEq/hour). Continuous electrocardiographic (ECG) monitoring is recommended for higher infusion rates [see *Dosage and Administration* (2.1, 2.2)].

5.2 Pulmonary Embolism due to Pulmonary Vascular Precipitates

Pulmonary vascular emboli and pulmonary distress related to precipitates in the pulmonary vasculature have been described in patients receiving admixed products containing calcium and phosphates or parenteral nutrition. The cause of precipitate formation has not been determined in all cases; however, in some fatal cases, pulmonary emboli occurred as a result of calcium phosphate precipitates. Precipitation has occurred following passage through an in-line filter; *in vivo* precipitate formation may also have occurred. If signs of pulmonary distress occur, stop the parenteral nutrition infusion and initiate a medical evaluation. In addition to inspection of the solution [see *Dosage and Administration* (2.1, 2.3)], the infusion set and catheter should also periodically be checked for precipitates.

5.3 Hyperkalemia

POTASSIUM PHOSPHATES INJECTION may increase the risk of hyperkalemia, including life-threatening cardiac events, especially when administered in excessive doses, undiluted or by rapid intravenous infusion [see *Warnings and Precautions* (5.1)]. Patients with severe renal impairment and end stage renal disease are at increased risk of developing life-threatening hyperkalemia, when administered intravenous potassium [see *Contraindications* (4)]. Other patients at increased risk of hyperkalemia include those with severe adrenal insufficiency or treated concurrently with other drugs that cause or increase the risk of hyperkalemia [see *Drug Interactions* (7.1)]. Patients with cardiac disease may be more susceptible to the effects of hyperkalemia.

Consider the amount of potassium from all sources when determining the dose of POTASSIUM PHOSPHATES INJECTION and do not exceed the maximum age-appropriate recommended daily amount of potassium. In patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to < 60 mL/min/1.73 m²), start at the low end of the dose range and monitor serum potassium, phosphorus, calcium, and magnesium concentrations [see *Dosage and Administration* (2.2, 2.4), *Use in Specific Populations* (8.6)].

When administering POTASSIUM PHOSPHATES INJECTION in intravenous fluids to correct hypophosphatemia, check the serum potassium concentration prior to administration. If the potassium concentration is 4 mEq/dL or more, do not administer POTASSIUM PHOSPHATES INJECTION and use an alternative source of phosphate [see *Dosage and Administration* (2.1)]. The maximum initial or single dose of POTASSIUM PHOSPHATES INJECTION in intravenous fluids to correct hypophosphatemia is phosphorus 45 mmol (potassium 71 mEq). The recommended infusion rate of potassium is 10 mEq/hour. Continuous electrocardiographic (ECG) monitoring is recommended for higher infusion rates of potassium [see *Dosage and Administration* (2.2)].

5.4 Hyperphosphatemia and Hypocalcemia

Hyperphosphatemia can occur with intravenous administration of potassium phosphates, especially in patients with renal impairment. Hyperphosphatemia can cause the formation of insoluble calcium phosphorus products with consequent hypocalcemia, neurological irritability with tetany, nephrocalcinosis with acute kidney injury and more rarely, cardiac irritability with arrhythmias.

Obtain serum calcium concentrations prior to administration and normalize the calcium before administering POTASSIUM PHOSPHATES INJECTION. POTASSIUM PHOSPHATES INJECTION is contraindicated in patients with hyperphosphatemia and/or hypercalcemia [see *Contraindications* (4)].

Monitor serum phosphorus and calcium concentrations during treatment with POTASSIUM PHOSPHATES INJECTION [see *Dosage and Administration* (2.2)].

5.5 Aluminum Toxicity

POTASSIUM PHOSPHATES INJECTION contains aluminum that may be toxic.

Aluminum may reach toxic levels with prolonged parenteral administration in patients with renal impairment. Preterm infants are particularly at risk for aluminum toxicity because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which also contain aluminum.

Patients with renal impairment, including preterm infants, who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum to levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Exposure to aluminum from POTASSIUM PHOSPHATES INJECTION is not more than 4.9 mcg/kg/day when:

- adults weighing at least 45 kg are administered the recommended maximum dosage of phosphorus (45 mmol/day) for parenteral nutrition.
- pediatric patients 12 years of age and older weighing at least 40 kg are administered the recommended maximum dosage of phosphorus (40 mmol/day) for parenteral nutrition [see *Dosage and Administrations* (2.4), *Description* (11)].

When prescribing POTASSIUM PHOSPHATES INJECTION for use in parenteral nutrition solutions containing other small volume parenteral products, the total daily patient exposure to aluminum from the admixture should be considered and maintained at no more than 5 mcg/kg/day [see *Use in Specific Populations* (8.4)].

POTASSIUM PHOSPHATES INJECTION for parenteral nutrition is not recommended in adults weighing less than 45 kg or pediatric patients less than 12 years of age or weighing less than 40 kg due to the risks of aluminum toxicity [see *Indications and Usage* (1.2)].

5.6 Hypomagnesemia

Intravenous infusion of phosphate has been reported to cause a decrease in serum magnesium (and calcium) concentrations when administered to patients with hypercalcemia and diabetic ketoacidosis. Monitor serum magnesium concentrations during treatment.

5.7 Vein Damage and Thrombosis

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.

When administered peripherally in intravenous fluids to correct hypophosphatemia, a generally recommended maximum concentration is phosphorus 6.4 mmol/100 mL (potassium 10 mEq/100 mL) [see *Dosage and Administration* (2.1)].

Parenteral nutrition solutions with an osmolarity of 900 mOsm/L or greater must be infused through a central catheter [see *Dosage and Administration* (2.3)].

5.8 Laboratory Monitoring

Monitor serum phosphorus, potassium, calcium and magnesium concentrations during treatment [see *Dosage and Administration* (2.2, 2.4)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Aluminum Toxicity [see *Warnings and Precautions* (5.5)]
- Hypomagnesemia [see *Warnings and Precautions* (5.6)]
- Vein Damage and Thrombosis [see *Warnings and Precautions* (5.7)]

The following adverse reactions in Table 3 have been reported in clinical studies or postmarketing reports in patients receiving intravenously administered potassium phosphates. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

TABLE 3: Adverse Reactions Reported in Clinical Studies or Postmarketing Reports with Intravenous Potassium Phosphates

System Organ Class	Adverse Reactions
<i>Metabolism and Nutrition Disorders</i>	pulmonary embolism due to pulmonary vascular precipitates [see <i>Warnings and Precautions</i> (5.2)], hyperkalemia [see <i>Warnings and Precautions</i> (5.3)], hyperphosphatemia [see <i>Warnings and Precautions</i> (5.4)], hypocalcemia [see <i>Warnings and Precautions</i> (5.5)], hypovolemia, and osmotic diuresis
<i>Cardiac Disorders</i>	hypotension, arrhythmia, heart block, cardiac arrest, bradycardia, chest pain, ECG changes [see <i>Warnings and Precautions</i> (5.1)], and edema
<i>Respiratory, Thoracic, and Mediastinal Disorders</i>	dyspnea [see <i>Warnings and Precautions</i> (5.2)]
<i>Renal and Urinary Disorders</i>	acute phosphate nephropathy (i.e., nephrocalcinosis with acute kidney injury), decreased urine output, and transition to chronic kidney disease [see <i>Warnings and Precautions</i> (5.4)]
<i>Gastrointestinal Disorders</i>	diarrhea, stomach pain
<i>Musculoskeletal and Connective Tissue Disorders</i>	weakness
<i>Nervous System Disorders</i>	confusion, lethargy, paralysis, paresthesia

7 DRUG INTERACTIONS

7.1 Other Products that Increase Serum Potassium

Administration of POTASSIUM PHOSPHATES INJECTION to patients treated concurrently or recently with products that increase serum potassium (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, digoxin, or the immunosuppressants tacrolimus and cyclosporine) increases the risk of severe and potentially fatal hyperkalemia, in particular in the presence of other risk factors for hyperkalemia [see *Warnings and Precautions* (5.2)]. Avoid use of POTASSIUM PHOSPHATES INJECTION in patients receiving such products. If use cannot be avoided, closely monitor serum potassium concentrations [see *Dosage and Administration* (2.2, 2.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the approved recommended dose of POTASSIUM PHOSPHATES INJECTION is not expected to cause major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with intravenous potassium phosphates.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-Fetal Risk

Phosphorus is an essential mineral element. Parenteral supplementation with potassium phosphates should be considered if a pregnant woman's requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation

Risk Summary

Phosphorus and potassium are present in human milk. Administration of the approved recommended dose of POTASSIUM PHOSPHATES INJECTION is not expected to cause harm to a breastfed infant. There is no information on the effects of potassium phosphates on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTASSIUM PHOSPHATES INJECTION and any potential adverse effects on the breastfed infant from POTASSIUM PHOSPHATES INJECTION or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of POTASSIUM PHOSPHATES INJECTION have been established in:

- pediatric patients 12 years and older as a source of phosphorus in intravenous fluids to correct hypophosphatemia when oral or enteral replacement is not possible, insufficient, or contraindicated.
- pediatric patients 12 years and older weighing at least 40 kg as a source of phosphorus for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

The safety of POTASSIUM PHOSPHATES INJECTION for parenteral nutrition has not been established in pediatric patients less than 12 years of age or in adolescents weighing less than 40 kg due to the risk of aluminum toxicity [see *Indications and Usage* (1.2), *Warnings and Precautions* (5.5)].

8.5 Geriatric Use

In general, dose selection of POTASSIUM PHOSPHATES INJECTION for an elderly patient should be cautious, starting at the low end of the dosing range because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. It may be useful to monitor renal function during treatment [see *Use in Specific Populations* (8.6)].

8.6 Renal Impairment

Potassium and phosphorus are known to be substantially excreted by the kidney and the risk of adverse reactions to POTASSIUM PHOSPHATES INJECTION may be greater in patients with impaired renal function [see *Warnings and Precautions* (5.3, 5.4, 5.5)].

POTASSIUM PHOSPHATES INJECTION is contraindicated due to the risk of hyperkalemia in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) or end stage renal disease [see *Contraindications* (4)].

In patients with moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73 m² to < 60 mL/min/1.73 m²), start at the low end of the dosage range and monitor serum potassium, phosphorus, calcium, and magnesium concentrations [see *Dosage and Administration* (2.2, 2.4)].

10 OVERDOSAGE

Hyperphosphatemia

Administration of excessive doses of intravenous potassium phosphates in intravenous fluids as a single dose ranging from approximately 50 to 270 mmol and/or at rapid infusion rates (over 1 to 3 hours) has resulted in death, cardiac arrest, cardiac arrhythmia (including QT prolongation), hyperkalemia, hyperphosphatemia, seizures, and tetany.

Hyperphosphatemia is particularly a risk in patients with renal failure. Hyperphosphatemia leads in turn to hypocalcemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure.

Hyperkalemia

Excessive administration of phosphates given as potassium salts may also cause hyperkalemia. Manifestations of hyperkalemia include:

- Disturbances in cardiac conduction and arrhythmias, including bradycardia, heart block, asystole, ventricular tachycardia, ventricular fibrillation
- Hypotension
- Muscle weakness including paresthesia, muscular and respiratory paralysis

Management

In the event of overdosage, discontinue infusions containing potassium phosphates immediately and institute general supportive measures, including ECG monitoring, laboratory monitoring, and correction of serum electrolyte concentrations, especially potassium, phosphorus, calcium, and magnesium.

11 DESCRIPTION

POTASSIUM PHOSPHATES INJECTION, USP, is a phosphorus replacement product containing phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL). It is a sterile, nonpyrogenic, concentrated solution containing a mixture of monobasic potassium phosphate and dibasic potassium phosphate in water for injection. It is supplied as a 15 mL partial fill single-dose glass vial.

Monobasic Potassium Phosphate is chemically designated KH₂PO₄, molecular weight 136.09, white, odorless crystals or granules freely soluble in water.

Dibasic Potassium Phosphate is chemically designated K_2HPO_4 , molecular weight 174.18, colorless or white granular salt freely soluble in water.

The solution is administered after dilution or admixing by the intravenous route.

Each mL contains 175 mg of monobasic potassium phosphate and 300 mg of dibasic potassium phosphate.

Each mL contains 3 mmol phosphorus (equivalent to 93 mg phosphorous) and 4.7 mEq potassium (equivalent to 184 mg of potassium). Note: 1 mmol of phosphorus is equal to 1 mmol phosphate. The pH is 6.5 to 7.5.

This product contains no more than 15,000 mcg/L of aluminum [see *Warnings and Precautions* (5.5)].

The osmolar concentration is 7.7 mOsmol/mL (calc).

12 CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Phosphorus in the form of organic and inorganic phosphate has a variety of biochemical functions in all organs and tissues, including critical roles in nucleic acid structure, energy storage and transfer, cell signaling, cell membrane composition and structure, acid-base balance, mineral homeostasis and bone mineralization.

12.3 Pharmacokinetics

Distribution

Approximately 85% of serum phosphates is free and ultra-filterable and 15% is protein-bound.

Elimination

Intravenously infused phosphates not taken up by the tissues are excreted almost entirely in the urine. Serum phosphorus is believed to be filterable by the renal glomeruli and the major portion of filtered phosphorus (greater than 80%) is actively reabsorbed by the tubules.

16 HOW SUPPLIED/STORAGE AND HANDLING

POTASSIUM PHOSPHATES INJECTION, USP: phosphorus 45 mmol/15 mL (3 mmol/mL) and potassium 71 mEq/15 mL (4.7 mEq/mL) as a clear and colorless solution supplied in a 15 mL single-dose glass vial (NDC 46287-024-15) in a single count carton (NDC 46287-024-15).

Store at 2°C to 8°C (36°F to 46°F). Do not freeze.

For storage of admixed solution see *Dosage and Administration* 2.2, 2.4.

17 PATIENT COUNSELING INFORMATION

Inform patients, caregivers or home healthcare providers of the following risks of POTASSIUM PHOSPHATES INJECTION:

- Serious Cardiac Adverse Reactions with Undiluted, Bolus or Rapid Intravenous Administration [see *Warnings and Precautions* (5.1)]
- Pulmonary Embolism due to Pulmonary Vascular Precipitates [see *Warnings and Precautions* (5.2)]
- Hyperkalemia [see *Warnings and Precautions* (5.3)]
- Hyperphosphatemia and Hypocalcemia [see *Warnings and Precautions* (5.4)]
- Aluminum toxicity [see *Warnings and Precautions* (5.5)]
- Hypomagnesemia [see *Warnings and Precautions* (5.6)]
- Vein Damage and Thrombosis [see *Warnings and Precautions* (5.7)]

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Drugs@FDA contains information about products *approved by the FDA* for human use in the United States since 1938, including:

- **Prescription** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#prescription_drug) products:
 - Brand-name drug products (for example, CRESTOR, LESCOL XL, LIPITOR, LIVALO, PRAVACHOL, ZOCOR), including **discontinued drugs** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#discontinued_drug) and drug products approved under "Submission Classification 'Type 6'" (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#submission_class)"
 - Generic drug products (for example, atorvastatin*), including **discontinued drugs** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#discontinued_drug)
 - Many **therapeutic biological products** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#ther_biological) (for example, CIMZIA, ENBREL, HUMIRA, REMICADE, and SIMPONI), including biosimilar products (for example, AMJEVITA, CYLTEZO, HADLIMA, and HYRIMOZ). (See biological products that are *not* included in Drugs@FDA under the heading "[What products are not in Drugs@FDA?](#)")
 - Medical gases
- **Over-the-counter (OTC)** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#OTC>) drugs:
 - Brand-name drugs (for example, ADVIL, MOTRIN)
 - Generic drugs (for example, ibuprofen*)

* Use the term "atorvastatin" when searching for "atorvastatin calcium tablets" and use the term "ibuprofen" when searching for "ibuprofen tablets."

3. What products are *not* in Drugs@FDA?

Drugs@FDA does *not* include information about the following FDA-approved products for human use, which are regulated by the **Center for Biologics Evaluation and Research** (<https://www.fda.gov/vaccines-blood-biologics>):

- Vaccines
- Allergenic products (for example, allergen extracts for diagnosis and treatment)
- Blood and blood products intended for infusion

- Plasma derivatives [for example, Albumin, Immune Globulin Intravenous (IGIV)]
- Cellular and gene therapy products (for example, KYMRIAH, MACI, YESCARTA, ZOLGENSMA)
- Products regulated by CBER under an NDA or an ANDA (for example, Plasma Volume Expanders, Platelet Additive Solutions)

Drugs@FDA does not include information about the following FDA-regulated products that do not require FDA approval to be sold in the United States:

- OTC drug products marketed under the **OTC drug monograph system** (<https://www.fda.gov/drugs/current-good-manufacturing-practices-cgmp-drugs-reports-guidances-and-additional-information/over-counter-otc-drug-monograph-process>). These products do not have applications (for example, bacitracin zinc ointment, diphenhydramine hydrochloride tablets.)
- **Dietary supplements** (<https://www.fda.gov/food/dietary-supplements>) (for example, St. John's wort, vitamin E)

Drugs@FDA also does not include information about the following products:

- Animal prescription and OTC drugs. See **Animal Drugs@FDA** (<https://animaldrugsatfda.fda.gov/adafda/views/#search>).
- Drug and biological products sold outside the United States that are not approved for marketing in the United States
- Drug and biological products under review at FDA for approval (investigational products)

4. Why doesn't Drugs@FDA include dietary supplements?

Dietary supplements (<https://www.fda.gov/food/dietary-supplements>), do not require FDA approval to be sold in the United States. (Drugs@FDA only includes information about FDA-approved drugs.) FDA's **Center for Food Safety and Applied Nutrition** (<https://www.fda.gov/Food/default.htm>) is responsible for FDA's oversight of dietary supplements.

5. What information is typically available for a product in Drugs@FDA?

The following information is typically available for a product in Drugs@FDA:

- Drug name(s), active ingredient(s), dosage form(s), route(s) of administration, and strength(s)
- The latest FDA-approved labeling and previously approved labeling:
 - For prescription products, Drugs@FDA typically includes the Prescribing Information and FDA-approved patient labeling when available (for example, Medication Guides, Patient Information, and/or Instructions for Use), and Drugs@FDA may include FDA-approved carton/container labeling
 - For OTC drugs, Drugs@FDA typically includes the carton/container labeling (for example, Drug Facts)
- Regulatory information including:
 - Application type: New Drug Application (NDA), Biologics License Application (BLA), Abbreviated New Drug Application (ANDA)
 - Application number
 - Company that sponsored the application
 - Approval letters and approval dates
 - Marketing status (for example, prescription, OTC, discontinued)
 - Submission classification
 - FDA and sponsor meeting minutes regarding the development of the product
 - Reference Listed Drug (RLD) and Reference Standard (RS) information
 - **Therapeutic Equivalence Codes** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#TE_codes) (TE Codes)
 - Therapeutically equivalent drug products
- Reviews by FDA staff that evaluate the safety and effectiveness of the product and a list of FDA staff involved in the review of the application

The majority of labeling, approval letters, FDA staff reviews, and other information listed above are available for FDA-approved prescription drug and biological products for human use since 1998 (see the exceptions under **"What products are not in Drugs@FDA"**?).

6. How can I search Drugs@FDA?

You can search Drugs@FDA in the following ways:

- Use the search box on the home page to search by:
 - Drug name(s)
 - Active ingredient(s)
 - Application number (NDA, ANDA, or BLA number)
- Browse by drug name (in alphabetical order) using the **A-Z Index** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=browseByLetter.page&productLetter=A&ai=0>). Unlike the search box results, the A-Z "Drug Name" search results for an active ingredient will not include brand name drugs for this active ingredient or drugs that contain this active ingredient and other active ingredient(s). For example, the search results for "LISINOPRIL" (using the A-Z "Drug Name" search) will not include PRINIVIL, ZESTRIL, or QBRELIS and will not include ZESTORETIC (lisinopril and hydrochlorothiazide tablets).
- Use the **"Drug Approval Reports by Month"** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?panel=1#collapseReports>) menu on the Drugs@FDA home page to find the following information by month:
 - All approvals and tentative approvals
 - Original NDA and original BLA approvals
 - Original ANDA approvals

- Supplemental approvals to NDAs and BLAs
- Tentative ANDA approvals

* For details about the scope of FDA-approved products for human use in Drugs@FDA, see "[What products are in Drugs@FDA?](#)" and "[What products are not in Drugs@FDA?](#)".

7. How do searches work in Drugs@FDA?

For a drug name or active ingredient search:

- You can type in all or part of the drug or active ingredient name.
- You must enter at least three characters.
- When you enter a partial-word search, Drugs@FDA searches for that string of characters (in the exact order you typed them) anywhere in a drug or active ingredient name. For example, if you enter "proz" you will retrieve a list of drugs that have that four-letter string somewhere in the brand name or somewhere in the active ingredient name:
 - CEFPROZIL (an active ingredient)
 - OXAPROZIN (an active ingredient)
 - PROZAC (a brand-name drug)
 - PROZAC WEEKLY (a brand-name drug)
 - CEFZIL (CEFPROZIL is the active ingredient)
 - DAYPRO (OXAPROZIN is the active ingredient)
 - DAYPRO ALTA (OXAPROZIN is the active ingredient)

If you enter **two words separated by a space**, Drugs@FDA will look for records containing both words, whether they occur next to or apart from each other, within the drug name or active ingredient name (shown inside parentheses). For example, if you enter "chlorpheniramine pseudoephedrine" you will retrieve:

- ADVIL ALLERGY SINUS (**CHLORPHENIRAMINE** MALEATE; IBUPROFEN; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- CHILDREN'S ADVIL ALLERGY SINUS (**CHLORPHENIRAMINE** MALEATE; IBUPROFEN; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- CHLOR-TRIMETON (**CHLORPHENIRAMINE** MALEATE; **PSEUDOEPHEDRINE** SULFATE)
- CODIMAL-L.A. 12 (**CHLORPHENIRAMINE** MALEATE; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- HYDROCODONE BITARTRATE, **CHLORPHENIRAMINE** MALEATE AND **PSEUDOEPHEDRINE** HYDROCHLORIDE (**CHLORPHENIRAMINE** MALEATE; HYDROCODONE BITARTRATE; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- ISOCOLOR (**CHLORPHENIRAMINE** MALEATE; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- **PSEUDOEPHEDRINE** HYDROCHLORIDE AND **CHLORPHENIRAMINE** MALEATE (**CHLORPHENIRAMINE** MALEATE; **PSEUDOEPHEDRINE** HYDROCHLORIDE)
- ZUTRIPRO (**CHLORPHENIRAMINE** MALEATE; HYDROCODONE BITARTRATE; **PSEUDOEPHEDRINE** HYDROCHLORIDE)

For application number searches:

- You must enter all the digits for the NDA, ANDA, or BLA number.
- You must enter three to six digits.

For example:

- NDA:
 - 211349
 - 20702 or 020702
 - 7513, 07513, or 007513
 - 004, 0004, 00004, or 000004
- ANDA:
 - 211058
 - 71617 or 071617
- BLA:
 - 761112

You cannot combine an application number with a drug or active ingredient name in a search (for example, searching for "fluoxetine 18936" will not return any results).

Note: The drugs that are listed on the "Search Results" page are not always related in terms of their chemical makeup or the conditions they treat and are not likely substitutable. They appear together because their brand names or active ingredient names contain the words you entered in the search box. Even if drugs have the same active ingredient, dosage form, and strength, it might not be safe to use one drug in place of the other. You should always consult with a healthcare provider to determine if one drug can be safely substituted for another.

8. How can I find out if a generic drug is available for a brand-name drug that is approved under a New Drug Application (NDA)?

Drugs@FDA can tell you if there is a [therapeutic equivalent](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#TE) (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#TE>), for a prescription innovator drug or prescription generic drug.

- On the home page, search by the name of the brand-name or generic drug.

- On the Search Results page, select the drug name. A panel will open and list one or more applications with the same drug name.

Search Results for "prozac"
Products listed on this page may not be equivalent to one another.

Click to see all applications containing the selected Drug Name.

PROZAC
PROZAC WEEKLY

Search Results for "prozac"
Products listed on this page may not be equivalent to one another.

Select an application to view its details.

PROZAC

- PROZAC (FLUOXETINE HYDROCHLORIDE) | NDA #018936 | CAPSULE;ORAL | Prescription | ELI LILLY AND CO
- PROZAC (FLUOXETINE HYDROCHLORIDE) | NDA #020101 | SOLUTION;ORAL | Discontinued | LILLY
- PROZAC (FLUOXETINE HYDROCHLORIDE) | NDA #020974 | TABLET;ORAL | Discontinued | LILLY

PROZAC WEEKLY

- If one or more **generic drugs** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#generic_drug) are available, you will see a panel titled "Therapeutic Equivalents for NDA xxxxxx." Click on the panel to see the **therapeutically equivalent** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#TE>) drug products, including generic drugs.

New Drug Application (NDA): 018936
Company: ELI LILLY AND CO
Drug Name(s):
• PROZAC (FLUOXETINE HYDROCHLORIDE)
• SARAFEM (FLUOXETINE HYDROCHLORIDE)

EMAIL

- Medication Guide
- Other Important Information from FDA

Products on NDA 018936

Approval Date(s) and History, Letters, Labels, Reviews for NDA 018936

Labels for NDA 018936

Therapeutic Equivalents for NDA 018936

9. How often do you update Drugs@FDA?

We update the Drugs@FDA database every day (sometimes several times throughout the day) with new information about approved drug and biological products. We typically add information to Drugs@FDA about approved drug and biological products within two business days of approval. This may include information from original NDAs/BLAs, efficacy supplements, or labeling supplements.

10. Where does the information in Drugs@FDA come from?

The information in Drugs@FDA comes from:

- Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)** (<https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>).
- The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) and other internal systems used by FDA staff to track information about approved applications, approved supplements, and tentative approvals.

11. How does Drugs@FDA compare with the Orange Book (<https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>)?

Drugs@FDA and the Orange Book share some content and retrieval capabilities, but Drugs@FDA does not replace the Orange Book. You can read about the origin and purpose of the Orange Book in the **Orange Book Preface** (<https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface>).

Drugs@FDA includes information and features that are **not** in the Orange Book:

- Tentative Approvals and "**Type 6** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#submission_class)" approvals
- Labeling, approval letters, FDA and sponsor meeting minutes regarding the development of the product, safety information, and reviews from FDA staff about the safety and effectiveness of the product
- **Therapeutic biological products** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#ther_biological) (regulated under BLAs) approved by CDER
- Tables of **therapeutically equivalent** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#TE>) products
- Tables of OTC drugs containing the same active ingredient, strength, dosage form, and route of administration
- Drug approval reports by month

The *Orange Book* includes information and features that are **not** in Drugs@FDA:

- Patent and exclusivity information
- In the *Orange Book*, you can search by:
 - applicant (company)
 - dosage form (for example, tablet, capsule)
 - route of administration (for example, oral, subcutaneous, intravenous)
 - patent number
- In the *Orange Book*, you can filter search results by prescription (Rx), OTC, and discontinued drugs.

12. How does Drugs@FDA compare with the *Purple Book* (<https://purplebooksearch.fda.gov/>)?

Drugs@FDA and the Purple Book share some content and retrieval capabilities for products regulated by the Center for Drug Evaluation and Research (CDER), but Drugs@FDA does not replace the Purple Book. You can learn more about the Purple Book and its use on the About Purple Book webpage.

Drugs@FDA includes information and features that are **not** in the Purple Book:

- Labeling, approval letters, and information and reviews from FDA staff about the safety, purity and potency (safety and effectiveness) of the product
- "**Type 6** (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#submission_class)" "Type 9," or "Type 10" approvals
- **Drugs approved under NDAs** (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page#NDA>)

The Purple Book includes information and features for biological products regulated by CDER that are **not** in Drugs@FDA:

- Exclusivity information
- The Purple Book has simple and advanced search capabilities and you can search by:
 - proprietary (brand) name
 - nonproprietary (proper) name
 - applicant (company)
 - dosage form (for example, injection)
 - product presentation (for example auto injector, pre-filled syringe, vial)
 - route of administration (for example, subcutaneous, intravenous)
 - strength
- In the Purple Book, you can sort search results using more than 20 different properties including, licensed, revoked, name, applicant, product presentation, BLA number, etc.
- The Purple Book also includes FDA-licensed biological products regulated by the Center for Biologics Evaluation and Research

13. How are BLAs that were formerly approved under an NDA and subsequently deemed a BLA on March 23, 2020, displayed on drugs@FDA?

On March 23, 2020, an approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act), as required by section 7002(e)(4)(A) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). If an application for a biological product was submitted under section 505 of the FD&C Act, filed not later than March 23, 2019, and not approved as of March 23, 2020, section 7002(e)(4)(B) of the BPCI Act (added by section 607 of the Further Consolidated Appropriations Act, 2020) provides that if such an application is approved under section 505 of the FD&C Act before October 1, 2022, it will be deemed to be a license for the biological product under section 351 of the PHS Act upon approval.

Information about a product(s) approved in an NDA that was deemed to be a BLA continues to be included in Drugs@FDA. FDA assigned the same application number used for the approved NDA to the deemed BLA, so a search by "application number" will continue to lead to information on the application; however, the corresponding application type has changed from "NDA" to "BLA." The Drugs@FDA entry for an NDA that was deemed to be a BLA includes information related to the initial approval of the application under section 505 of the FD&C Act prior to the approved application being deemed to be a BLA.

Drugs@FDA no longer includes information on an application for a biological product that was approved under section 505 of the FD&C Act in circumstances in which the application holder notified FDA in writing that the product(s) was no longer marketed and requested that FDA withdraw approval of the application, and such withdrawal of approval was announced in a Federal Register notice with an effective date on or before March 23, 2020. For a list of withdrawn applications for biological products, see <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act>. (<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act>)

For additional information, see FDA's guidance on [The "Deemed to Be a License" Provision of the BPCI Act: Questions and Answers](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deemed-be-license-provision-bpci-act-questions-and-answers) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deemed-be-license-provision-bpci-act-questions-and-answers>).

14. What do the submission classification codes for NDAs and Review Designation codes stand for?

NDA classification codes, shown below, provide a way of categorizing NDAs to promote consistency across review divisions, enable analysis of trends, and facilitate planning and policy development. The NDA classification codes are not indicative of the extent of innovation or therapeutic value that a drug represents. For details see [MAPP 5018.2](https://www.fda.gov/media/94381/download) (<https://www.fda.gov/media/94381/download>).

*** NDA Submission Classifications**

Classification	Meaning
Type 1	New molecular entity
Type 2	New active ingredient
Type 3	New dosage form
Type 4	New combination
Type 5	New formulation or other differences
Type 6	New indication or claim, same applicant [no longer used]
Type 7	Previously marketed but without an approved NDA
Type 8	Rx to OTC
Type 9	New indication or claim, drug not to be marketed under type 9 NDA after approval
Type 10	New indication or claim, drug to be marketed under type 10 NDA after approval
Type 1/4	Type 1, New molecular entity, and Type 4, New combination
Type 2/3	Type 2, New active ingredient, and Type 3, New dosage form
Type 2/4	Type 2, New active ingredient and Type 4, New combination
Type 3/4	Type 3, New Dosage Form, and Type 4, New combination
Type 4/5	Type 4 New Combination and Type 5 New Formulation or New Manufacturer

Review designations for NDAs, BLAs, and efficacy supplements can be 'priority' or 'standard'.

- 'Priority' review designation is assigned to NDAs, BLAs, and efficacy supplements for drugs that treat serious conditions and provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies.
- 'Standard' review designation is assigned to applications and efficacy supplements for drugs that do not meet the priority review designation criteria. **For more information about the priority and standard designations, see MAPP 6020.3 (<https://www.fda.gov/media/72723/download>).**

15. Can I get a copy of the Drugs@FDA database?

Yes. Please see '[Drugs@FDA Data Files \(<https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files>\)](https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files)' for information about the database tables and a link to the compressed file for downloading. The file does not include the scripts (programming) we use to produce the online version of Drugs@FDA. We provide this technical information for users who are familiar with working with databases or spreadsheets.

16. How can I get further assistance?

- **For general drug information please contact FDA's Division of Drug Information (DDI).**
 - Phone: Toll Free (855) 543-3784 or (301) 796-3400
 - Fax: (301) 431-6353
 - Email: druginfo@fda.hhs.gov (<mailto:druginfo@fda.hhs.gov>)
 - Mail:
 - Office of Communications
 - 10001 New Hampshire Ave
 - Hillandale Building, Room 4147
 - Silver Spring, MD 20993
- **For technical questions about the Drugs@FDA site, please use our [Drugs@FDA Comments and Feedback form \(<https://www.accessdata.fda.gov/scripts/email/cder/commentdrugcat.cfm>\)](https://www.accessdata.fda.gov/scripts/email/cder/commentdrugcat.cfm).**