

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Par Health, Inc.  
Petitioner,  
v.

InfoRLife, S.A.  
Patent Owner,

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Case IPR2026-00036  
Patent No. 12,370,153

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**DECLARATION OF MICHAEL MAURIN, R.Ph., Ph.D., IN SUPPORT OF  
POST-GRANT REVIEW OF U.S. PATENT 12,370,153**

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1. I, Michael B. Maurin, R.Ph., Ph.D., understand that Par Health, Inc. (“Par”) is petitioning for Post-Grant Review (“PGR”) of U.S. Patent No. 12,370,153 (“the ’153 patent,” Ex. 1001) and requests that the United States Patent and Trademark Office (“PTO”) cancel claims 1–23 of the ’153 patent as unpatentable. The following discussion and analysis provide my opinions as to why claims 1–23 are anticipated and/or would have been obvious to a person of ordinary skill in the art.

## **I. BACKGROUND AND QUALIFICATIONS**

### **A. Educational Background**

2. I earned a Bachelor of Science degree in Pharmacy from the University of Pittsburgh, School of Pharmacy in 1983. In April 1988, I received a Ph.D. in Pharmaceutical Sciences from the University of Kentucky, College of Pharmacy, Division of Pharmaceutics.

3. I was an award-winning graduate and a recipient of University of Pittsburgh and Pennsylvania scholarships during my undergraduate studies. I completed a fifth year elective in parenteral products.

4. While pursuing my Ph.D. at the University of Kentucky, my research focused on the application of the understanding of physical, chemical, and biopharmaceutical properties to dosage form design. I received an academic scholarship from the University of Kentucky, a MENSA scholarship, and a graduate

student research award from the American Pharmaceutical Association Foundation at the 1987 joint Japan-United States Congress of Pharmaceutical Sciences.

**B. Professional Experience**

5. I am Co-Founder and Vice President of Maurin Healthcare Consulting, which provides consulting services that span the pharmaceutical development process from the screening and identification of new chemical entities through the development and manufacture of stable, bioavailable, commercially manufacturable, and registerable dosage forms for use in clinical trials and regulatory submissions.

6. My work began at DuPont, where I started in 1985 as a summer intern, and in 1988 as a Research Pharmacist. DuPont was acquired by Bristol-Myers Squibb (“BMS”) while I worked there. Over time, I received several promotions, each with increasing responsibility in the Pharmaceutical Research and Development Department. Ultimately, I was promoted to Director of Biopharmaceutics and Basic Pharmaceutics, the position I held when I left DuPont. At DuPont, I was recognized in the top 2% of the scientific contributors and received dozens of internal awards.

7. I founded QS Pharma in 2002 after leaving BMS. QS Pharma was a contract research organization that delivered a broad range of pharmaceutical product development and testing services to biopharmaceutical and pharmaceutical

companies on a global basis. I grew QS Pharma to forty-nine employees in a 48,000 sq. ft. facility. I served as Vice President and remained with QS Pharma through its successful acquisition by and integration into the WIL Research Holding Co. through 2008.

8. I serve on the Editorial Advisory Board for the Journal of Pharmaceutical Sciences, for which I was recognized for editorial excellence in 2003, 2004, 2005, 2014 and 2025. I previously served on the Editorial Advisory Board for The American Association of Pharmaceutical Scientists (“AAPS”) Journal (1999 to 2005); the Product Quality Research Institute, Biopharmaceutics Technical Committee, Oral Biopharmaceutics of Immediate Release Products Working Group (2000 to 2002); the National Institute of Health, National Cancer Institute Expert Panel Reviewer for RFP “Development of Dosage Forms and Delivery Systems for Antitumor Agents” (2002); the International Union of Pure and Applied Chemistry, Division of Chemistry and Human Health, Medicinal Chemistry Section, Delegate to the Pharmaceutical Salt Selection Working Party (1998 to 2001); and the Editor for the Americas for Drug Stability (1995 to 1999).

9. I am a registered pharmacist in Pennsylvania and Delaware.

10. My educational background, work experience, and a list of my publications are set forth in my curriculum vitae which is attached as Ex. 1003.

**II. MATERIALS CONSIDERED**

11. In formulating my opinion and preparing this declaration, I have reviewed and/or relied upon the documents cited in this declaration and/or listed in the table below:

<b>Exhibit No.</b>	<b>Exhibit Description</b>
1001	U.S. Patent No. 12,370,153 (“’153 patent”)
1002	File History of the ’153 patent
1003	Declaration of Dr. Michael Maurin, R.Ph., Ph.D.
1004	Curriculum Vitae of Dr. Michael Maurin, R.Ph., Ph.D. (“Maurin CV”)
1005	Ketamine (Biomed) New Zealand Data Sheet (“Biomed”)
1006	REMYNTOX: THE SCIENCE AND PRACTICE OF PHARMACY (Adeboye Adejare ed., 23rd edition 2021) (“Remington 2021”)
1007	SealedAir Nexcel Product Data Sheet (M312 Film) (“M312 Film Data Sheet”)
1008	SealedAir Nexcel Product Data Sheet (M315 Film) (“M315 Film Data Sheet”)
1009	Sylvie Ponlot, <i>Sensitive Molecules Get Their Own Bags</i> , 7 FLEXMAG 1 (2014) (“Technoflex Inerta”)
1010	Sinner & B.N. Graf, Ketamine in Handbook of Experimental Pharmacology 313 (Springer Verlag Berlin Heidelberg ed. 2008)
1011	R. Craven, <i>Ketamine</i> , 62 (Suppl. 1) ANAESTHESIA 48 (2007)

<b>Exhibit No.</b>	<b>Exhibit Description</b>
1012	Rachel Quibell et al., <i>Ketamine Therapeutic Reviews</i> , 41 J. PAIN & SYMPTOM MANAGEMENT 640 (2011)
1013	Anirudda Pai & Mark Heining, <i>Ketamine</i> , 7 CONTINUING EDUCATION IN ANAESTHESIA, CRITICAL CARE & PAIN 59 (2007)
1014	Ketalar® Injection Label, dated 2012
1015	REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 19th edition 1995)
1016	FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, U.S. Dept. of Health & Human Servs., FDA (Sept. 2004)
1017	International Council for Harmonization (ICH) Guideline Q4B Annex 8 (June 21, 2017)
1018	European Pharmacopoeia 6.0, Chapter 2.6, Sterility: 2.6.1. (“Ph. Eur. 2.6.1”)
1019	USP <659>, Revision Bulletin, dated May 2017
1020	European Medicines Agency, Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (Mar. 2019)

### **III. LEGAL STANDARDS**

12. As I am not an attorney, a patent lawyer, nor an expert in patent law, the below legal standards are set forth as explained to me by counsel for Par. I have relied upon these legal principles in forming the opinions set forth in this declaration.

#### **A. Claim Construction**

13. I understand from counsel that patents include dependent and independent claims, and that a dependent claim references back to a prior claim and recites additional limitations. I further understand that the dependent claim, then, will include all limitations of the prior claim being incorporated into the dependent claim.

14. I understand that a patent claim is to be understood from the perspective of a person of ordinary skill in the art (“POSA”) to the subject matter of the patent. The POSA is a hypothetical person or a team of persons with a level of skill commensurate with that of an ordinary practitioner in the relevant field at the time the patent application at issue was originally filed.

15. I also understand that a POSA is presumed to be familiar with all prior art relevant to the claimed subject matter and may possess the combined knowledge of those skilled in the various fields pertinent to the invention. Additionally, I understand that the ’153 patent has an earliest available filing date of July 12, 2023, the date on which the provisional application to which it claims priority was filed.

16. It is my further understanding that the term “ordinary skill” may take into consideration one or more of the following factors, in assessing the level of skill of the POSA for the field of the ’153 patent: (1) the educational level of the named inventor(s); (2) the type of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) educational level of active workers in the field.

17. I understand from counsel that with regard to claim construction, the claims should be given their plain and ordinary meaning as understood by the POSA. This still requires that the claims should be read in the context of the specification and the other claim limitations, and each limitation should be given effect. I understand that there are two situations in which the plain and ordinary meaning would not be applied: when the patentee has defined the term themselves by acting as their “own lexicographer” or where they have disavowed claim scope.

18. I understand that a patentee acts as its own lexicographer when a patentee provides a definition in the specification, and that is that definition—rather than the term’s plain and ordinary meaning—that will govern claim construction. The redefinition need not be explicit; a patentee can implicitly redefine a term if the implied definition is so clear that a person of ordinary skill in the art would understand it to be equivalent to an explicit definition.

19. I further understand that statements made during the prosecution of the patent by the applicant are relevant to interpreting the definition of claim terms.

20. While not as relevant as either the specification or prosecution history of the patent, dictionaries and treatises may be referred to for the interpretation of claim terms.

**B. Anticipation**

21. I understand from counsel that a patent claim may be declared invalid if it is anticipated by the prior art.

22. I understand from counsel that each patent claim is to be presumed valid, and should only be considered invalid if there is clear and convincing evidence that the patent claim is invalid. I further understand from counsel that the validity or invalidity of each claim is to be considered separately.

23. I understand that a patent claim may be declared invalid due to anticipation of a patent claim if each element is described in a single prior art reference, expressly or inherently. I understand that an element of a patent claim is inherent in a prior art reference if the element must necessarily be present and would be recognized by one of ordinary skill in the art as being necessarily present. Regarding inherent disclosures, I understand that one or more secondary references may be used to show the inherency of a claimed element in a prior art reference. I understand, however, that inherency cannot be established by mere possibilities.

24. I further understand that a prior art reference anticipates a claimed range if that prior art reference discloses a value within the claimed range.

**C. Obviousness**

25. I understand that a patent claim may be declared invalid if the elements of the patent claim are obvious to a person of ordinary skill in the art as of the effective filing date of the patent claim, in view of the prior art.

26. I understand that a patent claim may be invalid as obvious if the subject matter of the patent claim would have been obvious to a person of ordinary skill in the art in view of a prior art reference or disclosure or a combination of prior art references/disclosures. I understand that the scope and content of the prior art is formed by all prior art—including prior printed publications, items sold or offered for sale, items in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention, for the obviousness analysis. I further understand that a prior art reference renders a claimed range obvious if that prior art reference discloses a value within the claimed range.

27. I further understand that an applicant may itself, in the specification or during prosecution of the patent, identify prior art, and that the applicant's identification amounts to an admission regarding that prior art, which may be taken into consideration for anticipation and obviousness determinations.

28. I understand that whether a patent claim would have been obvious requires an analysis of the scope and content of the prior art and a comparison of the prior art to the patent claims in light of the level of ordinary skill in the pertinent art. I further understand that evidence of secondary considerations may be used to overcome the showing of obviousness, as long as they have a nexus to the claims. Such secondary considerations may include commercial success, long-felt but unresolved need, copying, failure of others, praise for the invention, and unexpected results, and a few are described below.

**1. Secondary Considerations – Unexpected Results**

29. I understand that to establish unexpected results, the applicant must demonstrate that the claimed invention differs from the prior art to such an extent that the difference is truly unexpected, rather than merely a predictable variation. I understand that this comparison must take place in comparison between the claimed invention and the closest prior art.

30. Evidence of unexpected results may take several forms, including: (1) a greater than expected result, where the combination achieves outcomes beyond what would have been predicted from the individual components or prior art teachings; (2) superiority in a property shared with the prior art; (3) the presence of an unexpected property not possessed by the prior art; or (4) the absence of a property that the prior art would have predicted the invention to possess.

31. I further understand that the unexpected results must be commensurate in scope with the claims which the evidence is offered to support.

32. I understand that the difference must be a difference in kind and not merely a difference in degree.

## **2. Secondary Considerations – Teaching Away**

33. I understand that in order to show a prior art reference teaches away from the claimed invention, the prior art would need to provide that the proposed solution would not work, which would discourage the POSA from pursuing that solution or to take a different approach. I understand that prior art that teaches away from the claimed invention can create skepticism in industry participants regarding the viability of the proposed invention. I further understand that in order to be considered for the purpose of nonobviousness, such skepticism must be expressed before learning of the claimed invention.

## **IV. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)**

34. Counsel has suggested the level of skill and experience that a POSA in the field would have possessed when the application for the ’153 patent was filed:

A person of ordinary skill in the art (“POSA” or “ordinary artisan”) at the relevant time (*e.g.*, the July 12, 2023, filing date of the ’225 provisional application), would have been an individual or team of individuals working together to make pharmaceutical products, such as who possess a doctoral degree in pharmaceuticals, chemistry, such as pharmacology or pharmacy, or chemical engineering who has several years of practical experience with formulation of injectable drug delivery products, or someone possessing a Bachelors or Master’s

degree in one or more of the preceding disciplines but with a correspondingly greater level of experience with formulating injectable drug delivery products.

I agree with counsel's definition of a POSA and adopt it for the purpose of the analyses and opinions set forth in this report.

35. Based on my professional background and expertise, as set forth above in Section I and as further detailed in my curriculum vitae (Ex. 1003), I qualified as a POSA as of July 12, 2023, and I am otherwise very well aware of, and understand, the knowledge and experience of a POSA as of July 12, 2023. I have applied this level of knowledge to the opinions set forth herein.

## **V. TECHNICAL BACKGROUND AND STATE OF THE ART**

### **A. Ketamine**

36. (RS)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride ("ketamine hydrochloride") was first synthesized in 1962, and has been used as an anesthetic agent, as acknowledged by the '153 patent (Ex. 1001 at 1:37-43) since at least 1970. Ex. 1010 at 313, 314. It is a noncompetitive high affinity N-methyl-D-aspartate ("NMDA") receptor antagonist, with a mechanism of action primarily due to antagonism of NMDA receptors in the central nervous system. *See* Ex. 1011 at 48. The NMDA-glutamate receptor is a calcium channel which is involved in the development of neurons which transmit pain signals. Ex. 2012 at 640. Ketamine is a potent NMDA-receptor-channel blocker, effectuating analgesic

properties. *Id.*; see also Figure depicting the position at which ketamine blocking occurs (PCP) (below).

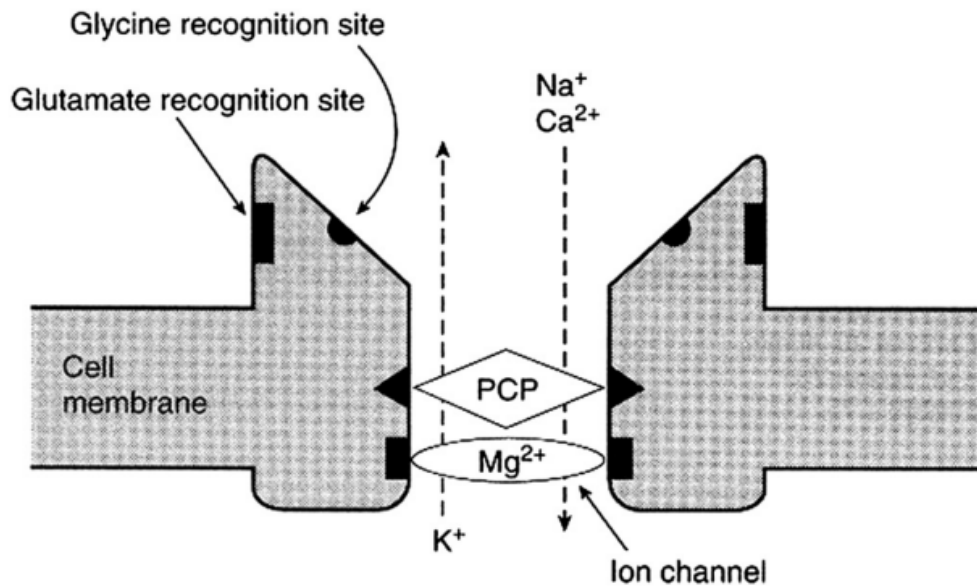
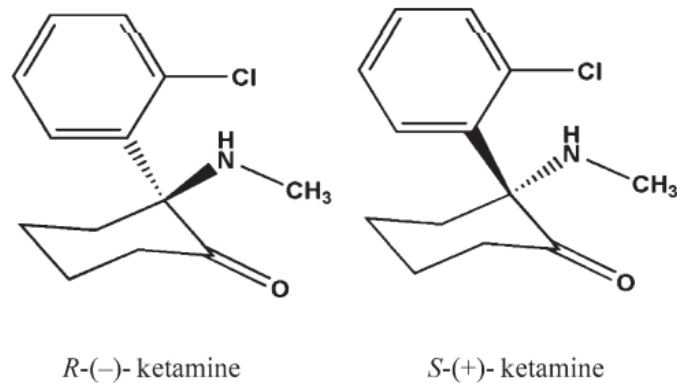


Figure. Diagram of NMDA (excitatory) receptor-channel complex. The channel is blocked by Mg<sup>2+</sup> when the membrane potential is at its resting level (voltage-dependent block) and by drugs that act at the phencyclidine (PCP) binding site in the glutamate-activated channel, e.g., dextromethorphan, ketamine, methadone (use-dependent block).<sup>4</sup> Figure reproduced by permission of [palliativedrugs.com](http://palliativedrugs.com) Ltd.

Ketamine is regarded as a “potent analgesic.” *Id.* at 50

37. Ketamine has two isomers. The isomers of ketamine are enantiomers: mirror images of each other around the chiral center, in R-(-) and S-(+) orientations. The enantiomers of ketamine are pictured below.



**Fig. 1** The optical isomers of ketamine

Ex. 1013 at 59, 60.

38. Ketamine can be administered to a patient intravenously, intramuscularly, orally, rectally, or subcutaneously, because it is both water and lipid soluble. Ex. 1011 at 49. A comparison of oral to intravenous administration demonstrated that peak effect was delayed in the oral route (15-30 minutes compared to 1-5 minutes), and that oral route compared to intravenous administration had lower peak serum concentrations (1/5<sup>th</sup>) and lower bioavailability (16% compared to 90%). *Id.*

39. Intravenous administration of ketamine includes continuous intravenous infusion (“CIVI”). CIVI can take place over a period of hours or days. *See, e.g.* Ex. 1012 at 642. Regimens include specific amounts of ketamine/kg/hour to titrate as necessary or a “burst” if indicated:

*CIVI*<sup>47,80</sup>

- start with 50–200 microgram/kg/h and titrate as necessary *or*
- give a single “burst” of 600microgram/kg up to a maximum of 60 mg over 4 h (reduce dose by 30–50% in elderly/frail patients); monitor blood pressure at baseline and then hourly:
  - if necessary, repeat daily for up to 5 days
  - if no response to an infusion, increase the next dose by 30%
  - continue to titrate according to response and/or occurrence of undesirable effects
  - repeat the above if the pain subsequently recurs.<sup>57</sup>

*Id.* at 645.

40. Ketamine was available in mixtures of the isomers (racemic, meaning equal amounts of the (R) and (S) isomers) in concentrations of 10, 50, and 100 mg/mL in formulations which included a preservative, benzethonium hydrochloride. Ex. 1013 at 61. Enantiomerically pure compositions of 5 and 25 mg/mL concentrations of (S)-(+)-ketamine were also available in certain locations. *Id.*

41. It was observed that ketamine when used epidurally produced neurotoxicity, which was attributed to the preservative in epidural formulations. However, preservative-free ketamine could be used for epidural administration. Ex. 1011 at 49; Ex. 1013 at 61.

**B. Pharmaceutical Presentations of Ketamine Available**

42. Parenteral medications are those where the active pharmaceutical ingredient is provided to the patient in a non-oral route. They include injectable and infusion forms of medication.

43. Parenteral formulations of ketamine hydrochloride (a salt of ketamine) have been available in injectable and infusion forms in the United States for many

years, under the brand name Ketalar® Injection. Ketalar is a ketamine hydrochloride injection available as of 2012 which is a sterile solution in a vial for intravenous or intramuscular (i.m.) injection in concentrations containing the equivalent of either 10, 50, or 100 mg ketamine per milliliter and not more than 0.1 mg/mL Phemerol® (benzethonium chloride) as a preservative. Ex. 1014 at 1. The 100 mg/mL concentration of Ketalar has to be diluted with water, sodium chloride, saline, or dextrose in water solution prior to administration to patients. *Id.* at 4-5 (for example, “Note: The 100 mg/mL concentration of Ketalar *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for injection, USP, Normal Saline, or 5% Dextrose in Water.”).

44. The background of the patent acknowledges that there are ketamine injectable vials on the market in the U.S. which contain concentrated ketamine solution which must be diluted with sterile water for injection (WFI), a sodium chloride solution, saline, or a dextrose in water solution prior to administration to a patient. Ex. 1001 at 1:57-67; *see, e.g.*, Ex. 1014 at 1, 4-5.

45. The ketamine injectable vials marketed as of 2012 contained 10 mg/mL, 50 mg/mL, and 100 mg/mL vials in cartons of 10. Ex. 1014 at 4. These were the only commercially available forms of ketamine in the United States market. Ketalar was marketed as a sterile solution, which as stated above, was a concentrated vial product requiring dilution prior to injection. *Id.* at 1. Bedside or pharmacy

compounding in a hospital is known to introduce the potential for errors in dosing and administration and the possibility of contamination.

46. When drugs are administered intravenously using an infusion bag, the prescribed medication is diluted with a sterile solution and typically hooked near the patient from a pole. The bag itself is connected through a tube to a catheter and then into a patient's vein to administer its contents, for example, medication, nutrition, or electrolytes. For ketamine, *e.g.*, Ketalar, administration can occur through infusion methods as well as through direct intravenous injection. *Id.* at 4-5.

### C. Infusion Bags

47. An infusion bag holds the fluids that will be administered to the patient, as described above for Ketalar. An exemplary bag manufactured by Technoflex is pictured below.



Ex. 1009 at 6.

48. The body of an infusion bag can be made of multiple layers of medical grade plastics, and have various numbers and types of ports. Plastic films are used to make IV-bags. For example, the Technoflex Inerta® contains two ports, one of which has a twist off closure. Other types of bags and films may contain ports which have a rubber closure, or are sealed (such as that pictured on the left port of the Technoflex Inerta). They also have ports which allow for infusion of the drug, and often, sealing of the bag to prevent contamination.

49. Another exemplary infusion bag listed in the patent is pictured here<sup>1</sup>:



**D. Isotonicity of Intravenous Drug Products**

50. Formulators are aware that a drug intended for intravenous administration must be isotonic with body fluids, meaning that, in the case of ketamine administered by intravenous infusion, the solution has the same, or nearly the same, osmotic pressure as blood serum. A hypertonic solution has higher osmotic

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<sup>1</sup> <https://www.hosokawa-yoko.co.jp/product/lifescience-primarycontainers/> (accessed Feb. 25, 2026) (Polyelite EHC by Hosokawa)

pressure and when in contact with cells of lower osmotic pressure, water will exit the cell through osmosis. A hypotonic solution functions vice versa, it has lower osmotic pressure than the cell, and water will flow into the cell leading to rigidity of the cell wall. Both hypertonic and hypotonic solutions can cause problems when administered intravenously, including hemolysis, the busting of red blood cells that have swollen beyond the pressure they can handle.

51. A solution that is isotonic with red blood cells is thus required. An isotonic solution will not result in any osmosis of water into or out of the cell, so the “tone” of the cells is retained. Remington 1995 (Ex. 1015) confirms that “solutions to be injected into the blood should be made isotonic with erythrocytes.” Ex. 1015 at 208.

52. Methods common to the POSA for adjusting tonicity include freezing point depression method, the sodium chloride equivalent method and the isotonic solution V-value method. Common excipients used to make a solution isotonic (near physiological pH) include sodium chloride, dextrose, and glycerin. Ex. 1006 at 581.

**E. Sterile Drug Products**

53. Drug formulators are aware of and follow guidance from regulatory bodies and treatises regarding the preparation of drug products. With regard to parenteral drug products, treatises such as REMINGTON, THE SCIENCE AND PRACTICE

OF PHARMACY (Adeboye Adejare ed., 23rd ed. 2021) (“Ex. 1006”) provide that parenteral drugs must be sterile. *See* Ex. 1006 at 579.

54. FDA provides guidelines for “Sterile Drug Products Produced by Aseptic Processing” in order to meet good manufacturing practice (cGMP) regulations, while emphasizing the two routes for sterilizing drugs of aseptic processing and terminal sterilization. FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, U.S. Dept. of Health & Human Servs., FDA (Sept. 2004) (“Ex. 1016”), at 2-3 (“[i]t is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible.”). Remington 2021 echoes the FDA’s Guidance that the forms of sterilization are likewise limited: “[w]henver possible, the parenteral product should be sterilized within as short a time as possible after being sealed in its final container (terminal sterilization). . . . Many products, both pharmaceutical and biological, are affected adversely by temperatures required for thermal sterilization. Therefore heat-labile products should be sterilized by a nonthermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner, so that contamination is not introduced into the filtrate.” Ex. 1006 at 597.

55. Thus, sterile drugs may be prepared using terminal sterilization or aseptic processing techniques. There are different methods of terminal sterilization,

including heat sterilization, irradiation, and chemical sterilization. When a drug is subjected to heat sterilization, using a machine such as an autoclave, the drug is subjected to intensely high temperatures which kill contaminants in the product. When using terminal sterilization, consideration must be given to the container and the drug product itself to ensure that the active pharmaceutical ingredient does not degrade at those conditions, and that the container can withstand the intensity of the cycle without itself degrading and contaminating the product.

56. For formulations which cannot be terminally sterilized, they are required to follow aseptic processing techniques to obtain and maintain sterility. Aseptic processing is the preparation and filling of drugs under very specific cleanliness conditions to ensure the sterility of the drug is maintained throughout its manufacture and filling. A primary step for a drug too unstable for terminal sterilization is to undergo sterile filtration to remove particulate matter and/or microbial contamination from the formulation. Unlike terminal sterilization, which kills existing contaminants, filtration physically removes them as the microorganisms are adsorbed, retained on, or near, the matrix of the filter. In order to avoid reintroduction of microorganisms (i.e. to maintain the sterility of the formulation), all subsequent steps must be performed by aseptic processing. This includes donning a litany of personal protective equipment (PPE), using sterile

equipment, and rigorous environmental controls, among other requirements, all intended to reduce the possibility of contamination during manufacturing.

57. Thus, as Ketalar was marketed as a sterile solution, it would have undergone either terminal sterilization or aseptic filling, the two known means for achieving sterility.

58. Another intravenous ketamine product, manufactured by Biomed Limited, is offered for sale in New Zealand. The medical regulatory body in New Zealand is MedSafe. MedSafe relies on the British Pharmacopoeia, which incorporates the European Pharmacopoeia. The European Commission is a founding member of the International Council for Harmonization (ICH) which provides guidance on sterility testing. *See* Ex. 1017. A POSA would thus refer to the ICH Guidance and the European Pharmacopoeia for medicinal products formulated for marketing and sale in New Zealand.

59. The ICH Q4B Guidance states that in the European Union, the corresponding monograph regarding sterility tests in ICH regions is Ph. Eur. Chapter, Sterility: 2.6.1. Ex. 1017 at 4. Chapter 6.0 of the European Pharmacopoeia, 2.6.1 Sterility, specifies that parenteral preparations must be tested for sterility. *See* Ex. 1018 at 158 (specifying the number of items in a batch for parenteral preparations that must be tested for sterility). Thus, a parenteral preparation approved for sale in New Zealand must be sterile.

**VI. RELEVANT PRIOR ART**

**A. Ketamine (Biomed)**

60. Ketamine (Biomed) (“Biomed”) is a data sheet for a ketamine product manufactured by Biomed Limited and approved in New Zealand. Biomed is dated June 15, 2021 and is prior art to the ’153 patent. Biomed specifies that the product was first approved on May 5, 2011.

61. Biomed discloses a ketamine product with 100 mg per 100 mL of ketamine in an infusion bag. Ex. 1005 at 1, 10. Biomed discloses a “clear, colourless isotonic solution for injection or infusion” which “contains no preservative” and contains sodium chloride, water for injection, and ketamine hydrochloride, at a pH of 3.5 to 5.5 *Id.* Biomed discloses that “[e]ach 100 mL of Ketamine 100 mg per 100 mL contains ketamine hydrochloride equivalent to 100 mg ketamine base.” *Id.* at 1.

62. Biomed is indicated “as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. . . [F]or the induction of anaesthesia prior to the administration of other general anaesthetic agents . . . [or T]o supplement low-potency agents such as nitrous oxide.” *Id.* Biomed discloses that it could be administered by intravenous infusion or intravenous injection, and that increments of the full induction dose “may be repeated, as needed, for maintenance of anaesthesia.” *Id.* at 2.

63. Biomed discloses that it requires storage at or below 25° C, and that it is for single use only (any unused product should be discarded). *Id.* at 10-11. Biomed is available in a flexible 100 mL IV bag with overwrap, and in IV infusion bags has a shelf life of 24 months from the date of manufacture. *Id.* at 10.

**B. Ph. Eur. 2.6.1**

64. European Pharmacopoeia 6.0, Chapter 2.6, Sterility: 2.6.1. (January 2008) (Ex. 1018) is dated 2008 and is prior art to the '153 patent.

65. Ph. Eur. 2.6.1 discloses the biological tests for sterility set forth in the European Pharmacopoeia the purpose of which is “to provide an independent control analyst with the means of verifying that a particular material meets the requirements of the European Pharmacopoeia.” Ex. 1018 at 158. Ph. Eur. 2.6.1. specifies that parenteral preparations should be tested for sterility and the number of items in the batch for testing in order to assess compliance. *Id.* at 158 (Table 2.6.1.-3).

**C. 2019 Sterilization Guideline**

66. European Medicines Agency, Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (Mar. 2019) (Ex. 2020) is dated 2019 and is prior art to the '153 patent.

67. 2019 Sterilization Guideline is guidance for the selection of sterilization methods for sterile products, specifying when the aseptic processing alternative to terminal sterilization is acceptable. 2019 Sterilization Guideline

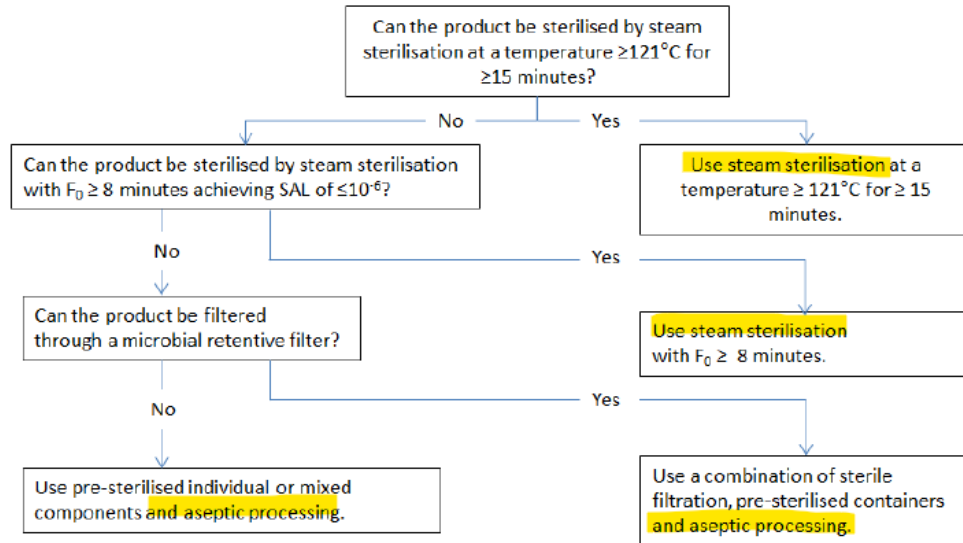
discloses that “terminal sterilisation provides the highest assurance of sterility and should be used whenever possible” and where that is not possible, “sterile filtration and/or aseptic processing under validated controlled conditions can be accepted.”

Ex. 2020 at 4.

68. 2019 Sterilization Guideline recognizes that “[s]terile filtration and aseptic processing,” the alternative to terminal sterilization, “are closely related and difficult to consider separately, since sterile filtration in most cases is followed by at least one aseptic processing step such as filling.” *Id.* 2019 Sterilization Guideline confirms that the two steps are thus conflated or used interchangeably, collectively representing aseptic processing as the alternative to terminal sterilization. *See id; see also id.* at 5 (referring to sterilisation as “Sterilisation by filtration and aseptic processing.”), 16.

69. 2019 Sterilization Guideline notes in decision trees that an aqueous finished product should be steam sterilized when possible, with filling by aseptic processing as the only other alternative.

**Figure 1 Decision tree for sterilisation choices for aqueous products**



See *id.* at 19 (Figure 1) (highlighting added).

**D. Remington 1995**

70. REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 19th edition 1995) (Ex. 1015) is dated 1995 and is prior art to the '153 patent.

71. Remington 1995 teaches that it is “desirable that solutions to be injected into the blood should be made isotonic with erythrocytes.” Ex. 1015 at 207-08. Remington 1995 teaches that to be isotonic with a cell requires no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. *Id.* at 613. Remington 1995 discloses that normal serum osmolality is 285 mOsmol/kg and acknowledges that the literature recognizes a range around 275-305

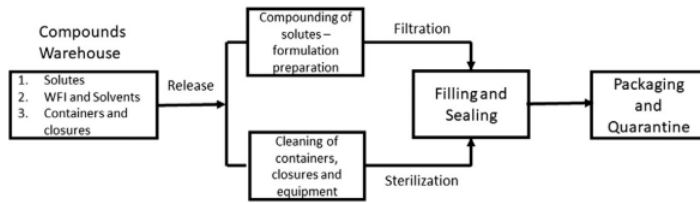
mOsmol/L as serum osmolality (recording 280-295 mOsmol/L, 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L, and 275-295 mOsmol/kg). *Id.* at 615.

72. Remington 1995 further discloses methods for adjusting tonicity, which include using sodium chloride to adjust tonicity. *See id.* at 620-21. For example, two methods, the freezing point depression method and the sodium chloride equivalent method follow the general steps of: “1. Identify a reference solution and the associated tonicity parameter. 2. Determine the contribution of the drug(s) and additive(s) to the total tonicity. 3. Determine the amount of sodium chloride needed [to make the solution isotonic] by subtracting the contribution of the actual solution from the reference solution.” *Id.* at 620.

**E. Remington 2021**

73. REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Adeboye Adejare ed., 23rd edition 2021) (Ex. 1006) is dated 2021 and is prior art to the '153 patent.

74. Remington 2021 discloses that the general considerations for development of parenteral products includes sterilization, listing terminal sterilization and aseptic processing or filtration. *Id.* at 579 (Table 29.3). Remington 2021 further discloses that “[d]epending on the product, either terminal sterilization in its final container or aseptic filling may be adopted” when a parenteral product is manufactured, referring to Figure 29.4. *Id.* at 587.



**FIGURE 29.4** General flow of operations in parenteral manufacturing.

*Id.* at 588 (Figure 29.4).

75. Remington 2021 teaches that a parenteral product sterilized by filtration must follow “stringent requirements” to prevent contamination during the subsequent filling step, a process termed “aseptic fill.” *Id.* at 595.

76. Remington 2021 further provides that:

Whenever possible, the parenteral product should be sterilized within as short a time as possible after being sealed in its final container (terminal sterilization). Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature on the stability of the product. Many products, both pharmaceutical and biological, are affected adversely by temperatures required for thermal sterilization. Therefore heat-labile products should be sterilized by a nonthermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner, so that contamination is not introduced into the filtrate.

*Id.* at 597.

**F. SealedAir Nexcel Product Data Sheet (M312 Film)**

77. SealedAir Nexcel Product Data Sheet for the M312 Film (Ex. 1007) is dated 2021 and is prior art to the '153 patent.

78. M312 Film Data Sheet discloses a clear, 5-layer, polyolefin-based extrusion for a film for medical and pharmaceutical applications. Ex. 1007 at 1-2. M312 Film Data Sheet discloses that it was “specifically developed to be a superior performing primary packaging film for terminally sterilized medical and pharmaceutical solutions.” *Id.* at 2. M312 Film Data Sheet further discloses that it was “designed to be chemically inert and have extremely low levels of extractables with a wide range of solutions – even under the demanding conditions of 121° C autoclave sterilization,” and that it was “designed for demanding packaging applications, such as saline, dextrose,” including “parenteral drugs.” *Id.* at 2.

79. M312 Film Data Sheet discloses that it had the following benefits:

- Wider sealing window for improved machinability and ease of handling;
- Robust film structure results in fewer leakers during production and distribution;
- Optimized barrier properties preserve drug efficacy;
- Extremely low extractables for broader drug compatibility and efficacy;
- Excellent low temperature abuse resistance;
- Excellent clarity;
- Heat sealable;
- PVC and phthalate free;
- Sterilizable at 121° C;

- Meets USP, EP, JP requirements, including USP class VI; and
- US DMF No. 9705.

*Id.*

**G. SealedAir Nexcel Product Data Sheet (M315 Film)**

80. SealedAir Nexcel Product Data Sheet for the M315 Film (Ex. 1008) is dated 2021 and is prior art to the '153 patent.

81. M315 Film Data Sheet discloses a clear, 4-layer, polyolefin-based extrusion for a film for medical and pharmaceutical applications. Ex. 1008 at 1-2. M315 Film Data Sheet discloses that it was “specifically developed to be a superior performing primary packaging film for terminally sterilized medical and pharmaceutical solutions.” *Id.* at 2. M315 Film Data Sheet further discloses that it was “designed to be chemically inert and have extremely low levels of extractables with a wide range of solutions – even under the demanding conditions of 121° C autoclave sterilization,” and that it was “designed for demanding packaging applications, such as saline, dextrose” including “parenteral drugs.” *Id.* at 2.

82. M315 Film Data Sheet discloses that it had the following benefits:

- Multilayered for superior abuse resistance;
- Tubular extrusion minimizes particulates;
- Excellent clarity;
- Extremely tough;

- PVC and plasticizer free;
- Sterilizable at 121° C;
- Excellent low temperature abuse resistance;
- Extremely low extractables;
- Meets USP and YBB regulatory requirements; and
- US DMF No. 9705.

*Id.* at 2.

**H. Technoflex Inerta**

83. Sylvie Ponlot, *Sensitive Molecules Get Their Own Bags*, 7 FLEXMAG 1 (2014) (Ex. 1009) is dated 2014 and is prior art to the '153 patent.

84. Technoflex Inerta discloses the line of Inerta® IV drug delivery bags manufactured by Technoflex. Inerta bags are polypropylene sterile bags which are aseptically filled. Ex. 1009 at 6. It can be fitted with either one or two tubes, with “boat ports” welded directly onto the bag body (annotated pictured below). *Id.*



A twist-off is welded to the tubular part of the first boat port, and the second is welded shut. *Id.*

85. Inerta bags are sterilized then placed in double packaging. *Id.*

## **VII. THE '153 PATENT**

86. The '153 patent (Ex. 1001) was filed as U.S. Application No. 18/770,514 on July 11, 2024, issued on July 29, 2025, and claims priority to U.S. Provisional Patent Application No. 63/513,225, filed on July 12, 2023. The '153 patent has 23 claims, of which I understand three claims are independent. I have reproduced the claims below.

1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the ketamine product is sterile and ready-to-use (RTU), wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and

wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C.

2. The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.

3. The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.

4. The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.

5. The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.

6. The ketamine product of claim 4, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.

7. The ketamine product of claim 4, wherein the closure comprises a plastic material.

8. The ketamine product of claim 4, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

9. The ketamine product of claim 7, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

10. The ketamine product of claim 4, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

11. The ketamine product of claim 4, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

12. The ketamine product of claim 4, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises polypropylene styrene-block copolymer.

13. The ketamine product of claim 4, wherein the infusion bag is contained with an overwrap.

14. The ketamine product of claim 13, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

15. The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

16. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C.

17. The ketamine product of claim 16, wherein the tonicity adjustment agent comprises sodium chloride,

dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

18. The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

19. The ketamine product of claim 1, wherein the ketamine content of the aqueous ketamine solution after accelerated storage at  $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / <25\%$  RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\%$  RH  $\pm 5\%$  RH is 97% or greater compared to the ketamine content before storage.

20. A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

21. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, wherein the ketamine solution is contained in an infusion bag, wherein the ketamine product has been aseptically filled, and wherein the ketamine product is sterile and ready-to-use (RTU), and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between  $15\text{-}30^{\circ}\text{C}$ .

22. The ketamine product of claim 16, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

23. The ketamine product of claim 21, wherein the ketamine or a pharmaceutically acceptable salt thereof is

chemically stable following 24 months of storage at 25°C  
± 2°C with relative humidity (RH) at 40% ± 5%.

**A. The Specification of the '153 Patent**

87. The specification of the '153 patent describes the alleged invention as a sterile, ready-to-use, stable aqueous solution of ketamine or a pharmaceutically acceptable salt thereof suitable for direct intravenous infusion to a patient in need of anesthesia for a diagnostic or surgical procedure. Ex. 1001 at Abstract, 1:15-20, 18:60-64.

88. The background of the '153 patent describes previously existing commercially available ketamine formulations approved by the FDA. In the United States, the most common ketamine products for injection were concentrated vials which required dilution prior to administration to the patient. *Id.* at 1:58-67. The specification further characterized ketamine formulations that were commercially available and approved by the FDA in the U.S. contained benzethonium chloride as a preservative. *Id.* at 1:34-36. The patent describes a few limitations of these vials, including that they needed to be used immediately after dilution, and that the vials were single-use and required disposal after opening even if the entire contents of the vial were not required. *Id.* at 1:63-2:2.

89. The '153 patent describes other limitations and shortcomings of the prior single-use concentrated ketamine solution vials as having additional costs and inconvenience, the risk of potential contamination due to inadvertent medical error,

and limited stability prohibiting long-term storage. *Id.* at 2:24-29. The patent alleges a ready to use dosage of a stable, preservative-free ketamine solution would overcome the issues in the existing products. *Id.* at 2:40-44.

90. The background of the '153 patent further discusses that the container closure for a product for parenteral use should take into consideration drug product formulation properties, dosage, type of application, stability, including stability when subjected to extreme conditions (such as terminal sterilization), sterility, container closure integrity, storage conditions and duration, and end-user friendliness. *Id.* at 1:48-54. This is to ensure compliance with storage and handling specifications for maintaining functionality and drug delivery accuracy. *Id.* at 1:44-48.

91. The '153 patent discloses a premixed formulation of ketamine, or a pharmaceutically acceptable salt thereof, also containing a tonicity adjusting agent, a pH adjusting agent, and water for injection, in an intravenous bag or infusion container. *Id.* at 2:49-63, 7:28-34. The solution is free from any antimicrobial or preservative, such as benzethonium chloride. *Id.* at 7:28-34, 19:9-14. The specification states that in certain aspects, the pH of the aqueous ketamine solution is about 3 to about 6. *Id.* at 3:11-16. The solution does not require dilution prior to administration to the patient. *Id.* at 2:52-57.

92. The patent acknowledges that the packaging of the product can affect the condition of formulations. *Id.* at 2:31-40 (mentioning for the primary plastic packaging for the infusion container: compatibility with the contents, minimizing extractables and leachables, solvent-resistance and durability). The patent states that “[t]he packaging of a pharmaceutical product should desirably be stable and mutually compatible under terminal sterilization conditions, as packaging materials and terminal sterilization can affect the condition of different formulations.” *Id.* at 2:36-40. The specification of the ’153 patent describes the types of intravenous bags for use in the invention, including those commercially available as Polyelite EHC® film bags manufactured by Hosokawa, Inerta 103 manufactured by Technoflex, Nexcel brand M312 and M312A® films by SealedAir Corporation, and M312 films from other manufacturers. *Id.* at 8:17-41.

93. The specification states that the polyolefin film of the infusion bag may be a M312 film, such as Nexcel brand M312A film manufactured by SealedAir Corporation, an M315 film manufactured by SealedAir Corporation, an APP-series film manufactured by Polycine, such as APP-114S film, a polypropylene film, like those manufactured by Technoflex, such as an Inerta® film, e.g. Inerta 103, or a cycloolefin polymer with a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer, such as those manufactured by Hosokawa. *Id.* at 9:42-10:19.

94. The patent states that the foregoing commercially available films for use in the invention are stable, with low leachables, and without physical deformation during terminal sterilization. *See, e.g., id.* at 8:37-40,10:39-65.

95. The '153 patent discusses the processes of sterilization disclosed in U.S. Patent Nos. 5,439,643 and 8,617,467 as “a sterilizing agent or process is used to kill microbes and other pathogens to create a sterile final product” by methods such as steam sterilization, heat sterilization (e.g., autoclave), radiation treatment (e.g., Gamma, E-beam, ultraviolet), or by chemical sterilization (e.g., ethylene oxide). *Id.* at 10:41-49.

96. The '153 patent has five examples. Example 1 describes exemplary formulations containing ketamine hydrochloride, sodium chloride, and water for injection (1 mg/mL ketamine, Table 1; 2 mg/mL ketamine, Table 2), ketamine freebase, sodium chloride, and water for injection (1 mg/mL, Table 3; 2 mg/mL, Table 4).

97. Example 2 is a stability study seven days after terminal sterilization, testing ketamine assay and pH (Table 5). Example 3 describes stability studies comparing the ketamine solution with a commercially available concentrated ketamine solution product in multi-dose glass vials under accelerated (6 months) and long term (12 months) conditions (Tables 6, 7, 8, 9).

98. Example 4 describes stress studies on the exemplary formulations, intended to identify the likely degradation products (Tables 10-21 and Tables 22-23 (thermal stress)). Example 5 describes manufacturing process development.

**B. Arguments Made During the Prosecution History of the '153 Patent**

99. I have read and understand the prosecution history of the '153 patent and discuss below particular portions which are relevant to my analysis.

100. The examiner repeatedly denied the claims as anticipated by Ketalar or rendered obvious by Ketalar in view of Conrad, a reference regarding sterile bags of the drug fentanyl. The examiner described the identical disclosure in Ketalar of the claimed formulation (ketamine, sodium chloride, and water for injection), and on that basis found that the claimed stability limitations (chemical stability, number of particles of certain sizes, ketamine content after accelerated storage, and shelf life) and osmolality would be inherent to the formulation itself, and therefore disclosed in Ketalar though not set forth explicitly. (Ex. 1002 at 260-61). The examiner explained that Ketalar was described as a “sterile” and “USP Grade” product, such that it would have followed aseptic filling and/or terminal sterilization processes as also set forth in certain claim limitations. *Id.* at 261 (“sterility of a product is a known function of autoclaving to one of skill in the art, and FDA approved

injections/infusions for *in vivo* administration in humans are for sterile/aseptic products.”).

101. The examiner noted that with respect to the numerous limitations directed to the bag containing the ketamine formulation, “what is disclosed as subject matter in these claims, even per Applicant’s own specification is in fact commercially available infusion bags.” Non-Final Rejection, dated Oct. 23, 2024, at 5-7 (Ex. 1002 at 218-20); Final Rejection, dated Dec. 19, 2024, at 6-8 (*Id.* at 263-265).

102. The applicant disputed the examiner’s rejection(s) on the basis that Ketalar was not “ready-to-use,” but required dilution prior to administration. Reply to Non-Final Rejection, dated Nov. 25, 2024, at 7-8 (*Id.* at 240-41); Amendment With a Request for Continued Examination, Mar. 14, 2025, at 10-11 (*Id.* at 290-91). Once diluted, Ketalar required short-term disposal, allegedly not meeting the stability proposed by the claims of at least six months at 15-30°C. The applicant further argued this showed lack of reasonable expectation of success for a stable pre-diluted ready-to-use formulation of ketamine. The applicant also distinguished Ketalar on the basis that it contained a preservative, unlike the claimed formulation. Amendment With a Request for Continued Examination, Mar. 14, 2025, at 15-16 (*Id.* at 295-96).

103. The applicant also argued that the limitations were supported by the secondary considerations of unexpected results by comparison to the concentrated ketamine vial products which were available, and alleged that the prior art taught away from storing pre-diluted ketamine solution for prolonged periods. *Id.* at 243.

104. Following an interview between the examiner and the applicant on March 19, 2025, an agreement was reached indicating the claims were in condition for allowance if applicant agreed to amendments to the claims including removing certain stability limitations and adding the “no anti-microbial” and pH range limitations to the independent claims. Applicant indicated its agreement in a call on March 20, 2025, and a Notice of Allowance was issued.

### **VIII. CLAIM CONSTRUCTION**

105. I am not a patent lawyer or a patent law expert, and I am applying the legal principles as explained to me by counsel for the construction I should apply of the claims of the '153 patent. I understand that the claims terms should be given their plain and ordinary meaning as understood by a POSA, unless the patentee acted as its “own lexicographer” by expressly defining a term or when an applicant has disavowed some of the claim scope.

106. The claims contain the terms “ready-to-use (RTU)” (*see* claims 1, 16, and 21) to describe the ketamine product (claims 1 and 21) and the infusion container (claim 16). The patentee has acted as its “own lexicographer” by explicitly defining

this term in the specification. Therefore, my understanding of this term and the definition I applied when undertaking my analysis is: “premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration).” Ex. 1001 at 15:66-16:5. Though the patentee acted as its own lexicographer, I note that this construction is consistent with the plain and ordinary meaning of “ready-to-use” to the POSA. Preparing a solution for administration may include multiple steps, such as transferring the solution to a different container (vial to syringe, for example) or diluting a concentrated solution (syringe contents to infusion bag). A solution which is “ready” for “use” means it can be administered to the patient, and requires no further steps for administration. For a drug product typically requiring a dilution step, such as a concentrated drug product, that would necessarily require the solution to be premixed to the correct concentration. The POSA would recognize if a drug required dilution, that step would need to take place prior to administration of the drug product to the patient, but if that same drug was in a solution where it was already pre-mixed (not requiring dilution), it would be administered without prior manipulation steps and considered “ready-to-use.”

107. The definition set forth in the specification is consistent with the use of the term “ready-to-use” as it is applied throughout the specification. *See, e.g., id.* at 2:52-57 (“The ready-to-use premixed pharmaceutical compositions of ketamine of the present invention are formulated for administration to a patient, **without the need to reconstitute or dilute** the composition prior to administration, e.g., in a ready-to-use infusion bag (also referred to as a “ready-to-use bag”)); 15:61-64 (“For example, in contrast to non-premixed formulations of ketamine, the premixed compositions provided herein are suitable for administration to a patient **without dilution**”).

108. I understand that, even though the patentee defined the term itself, the prosecution history may also be relied on to define a term used in the claims with reference to how the applicant described their alleged invention. Multiple times throughout the prosecution history, the applicant defined its alleged invention consistent with the definition above, in distinguishing the claims from the prior art concentrated vials of ketamine:

- “The specification defines the term ‘ready-to-use’ or ‘ready to use’ as referring to ‘premixed compositions that are suitable for administration to a patient without further manipulation (e.g., a pharmaceutical formulation that is in the container from which the product is administered to the patient (such as an infusion bag or prefilled syringe) and does not require dilution or admixing before administration.’ (Paragraph [0075]).” Reply to Non-Final Office Action, dated Nov. 25, 2024, at 7 (Ex. 1002 at 240); *see also* Amendment With a Request For Continued Examination, dated Mar. 14, 2025, at 11 (Ex. 1002 at 330).

- “A ‘ready-to-use drug product’ is a term of art meaning ‘a drug product . . . from which the entire drug content of the container(s) is administered to the patient,’ which ‘may simplify the preparation and administration of a drug compared to preparing and administering an exact weight- or BSA-based dose to the patient.’” Citing FDA Guidance for Industry. Distinguishing over Ketalar because it is not sterile, ready-to-use, because it is a “concentrated product that must be manipulated to transfer it to an infusion container and diluted to an appropriate concentration—those steps compromise sterility and mean that the product Ketalar product is not ‘ready-to-use.’” Reply to Non-Final Office Action, dated Nov. 25, 2024, at 7-8 (Ex. 1002 at 240-41).
- Refuting the examiner’s broader interpretation of “ready-to-use” by indicating that the specification expressly defined the term (as set forth above) and citing to MPEP 2111.01(IV)(A) for the proposition that “[w]here an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim” to argue “[t]hus, the Office Action’s various different interpretations are unnecessary and irrelevant where the only definition that controls is the one that is expressly provided in the specification.” Amendment With a Request For Continued Examination, dated Mar. 14, 2025, at 10 (Ex. 1002 at 290).
- Distinguishing the alleged invention by concluding “the Office’s reliance on a dilution step means that the proposed modification to [Ketalar] results in something that does not meet the definition of ready-to-use required by the claims.” Amendment With a Request For Continued Examination, dated Mar. 14, 2025, at 14 (Ex. 1002 at 333).

109. For these reasons, both the specification and the prosecution history support the definition I set forth for the term “ready-to-use” in claims 1, 16, and 21 of the ’153 patent.

110. The claims also contain the term “chemically stable” (*see* claims 18, 22, 23) to describe the ketamine product (claims 1, 16, and 21). The patentee has acted as its “own lexicographer” for this term as well by also explicitly defining this term in the specification. Accordingly, I understand this term to have the definition

provided in the specification, which is what I applied for my analysis: “a chemical compound which retains its chemical structure and useful properties on a timescale of its expected usefulness. Specifically, the usefulness of the compound is maintained in the environment in which it is stored.” Ex. 1001 at 15:43-47. In the context of pharmaceutical formulations, the POSA would understand this definition to generally equate to “having an acceptable shelf life” of the product.

**IX. GROUND 1: ANTICIPATION OF CLAIMS 1, 3–5, 13 AND 18–20 BY KETAMINE (BIOMED)**

**A. Independent Claim 1**

- 1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection,**

111. Biomed describes a ketamine product available in New Zealand before the effective filing date which contains 100 mg/100 mL (i.e. 1 mg/mL) ketamine. Ex. 1005 at 1. The concentration is within the claimed range and thus anticipates the claimed range.

112. Biomed contains sodium chloride and water for injection and is an isotonic solution for infusion. Ex. 1005 at 1, 10. The '153 patent discloses that sodium chloride is a tonicity adjusting agent (see, e.g., Ex. 1001 at 3:8-10), consistent with the disclosure of Remington 1995 (“[t]he first two of these methods [of adjusting tonicity] can be used with a three step problem solving process based

on sodium chloride.”). Ex. 1015 at 620-21. Thus, Biomed anticipates the claimed limitations.

**2. wherein the ketamine solution is preservative-free and anti-microbial free,**

113. Biomed does not contain a preservative or an anti-microbial. Ex. 1005 at 1. The only excipients Biomed contains are sodium chloride and water for injection, and the label explicitly states that “[the formulation] contains no preservative.” *Id.* The POSA would understand that sodium chloride and water for injection are not preservatives or anti-microbials. Indeed, the ’153 patent discloses that sodium chloride is a tonicity adjusting agent (see, e.g., Ex. 1001 at 3:8-10), consistent with the disclosure of Remington 1995 (“[t]he first two of these methods [of adjusting tonicity] can be used with a three step problem solving process based on sodium chloride.”). Ex. 1015 at 620-21. Therefore, a POSA would understand that Biomed does not contain a preservative or an anti-microbial.

**3. wherein the ketamine product is sterile and ready-to-use (RTU),**

114. Biomed is available in a flexible 100 mL IV bag with overwrap. Ex. 1005 at 10. Biomed is administered by intravenous infusion. *Id.* at 2. The POSA would recognize that as an approved product in New Zealand for intravenous administration, Biomed would have needed to be sterile. Remington 2021 provides that sterilization is a consideration for the development of parenteral products,

generally, and Chapter 2.6.1 of the relevant regulatory guidance for New Zealand products, the European Pharmacopoeia, confirms that parenteral preparations “should be tested for sterility” to assess compliance with the European Pharmacopoeia. *See, e.g.*, Ex. 1006 at 579; Ex. 1018 at 158. There are no instructions for dilution prior to administration, thus a POSA would understand that Biomed is ready-to-use (RTU). Ex. 1005 at 2.

**4. wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5,**

115. Biomed is formulated as an acid (pH 3.5 to 5.5) solution. *Id.* at 1. The range of pH for Biomed overlaps with, and thus anticipates, the claimed range of a pH of the aqueous ketamine solution of about 3.5 to about 5.5.

**5. and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C.**

116. Biomed instructs that it should be stored at or below 25°C and not refrigerated or frozen, which a POSA would understand as overlapping with, and thus anticipating, the claimed range of 15-30°C. *Id.* at 10. Biomed discloses that it has a shelf life of 24 months for the 100 mg per 100 mL (*i.e.* 1 mg/mL) IV Infusion bags, which encompasses the claimed range of “a shelf-life of more than six months,” thus anticipating the claimed range. *Id.*

## 6. Conclusion

117. Based on the foregoing, it is my opinion that claim 1 of the '153 patent is anticipated.

### B. Dependent Claim 3

118. Dependent Claim 3 of the '153 patent recites: The ketamine product of claim 1, wherein the ketamine is at a concentration of about 1 mg/mL to about 2 mg/mL.

119. The concentration of the Biomed 100 mg/100 mL ketamine product (1 mg/mL) is within, and thus anticipates, the claimed range. *Id.* at 1. Therefore, it is my opinion that claim 3 of the '153 patent is anticipated.

### C. Dependent Claim 4

120. Dependent Claim 4 of the '153 patent recites: The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure.

121. Biomed is available in a flexible 100 mL IV infusion bag with overwrap. *Id.* at 10. Biomed is administered as an intravenous infusion, and there are no instructions that would indicate to a POSA that the product is not administered directly to the patient. *Id.* at 2. Thus, Biomed is intended to be directly administered to the patient. A POSA would immediately understand that any IV infusion bag containing an infusion solution administered directly to a patient would have to have

at least one port sealed with a closure to facilitate the administration. Therefore, it is my opinion that claim 4 of the '153 patent is anticipated.

**D. Dependent Claim 5**

122. Dependent Claim 5 of the '153 patent recites: The ketamine product of claim 1, wherein the aqueous ketamine solution has an osmolality of about 270-330 mOsmol/kg.

123. Biomed discloses that the infusion solution is isotonic and therefore discloses this limitation. *Id.* at 1. Isotonicity refers to the osmotic pressure of a solution: if in solution, human erythrocyte cells “maintain their ‘tone,’” i.e., are not hypertonic or hypotonic, the solution is said to be “isotonic.” Ex. 1015 at 207. Thus, the POSA would immediately understand that the Biomed product would need to have equal osmotic pressure to serum to reduce the risk of hemolysis.

124. Remington 1995 discloses that normal serum osmolality is 285 mOsmol/kg and acknowledges that the literature recognizes a range around 275-305 mOsmol/L as serum osmolality (i.e., isotonic) (recording 280-295 mOsmol/L, 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L, and 275-295 mOsmol/kg). *Id.* at 615. Therefore, a POSA would know that Biomed’s disclosure of an isotonic infusion solution is within, and thus anticipates, the claimed range of an osmolality of about 270-330 mOsmol/kg. Therefore, it is my opinion that claim 5 of the '153 patent is anticipated.

**E. Dependent Claim 13**

125. Dependent Claim 13 of the '153 patent recites: The ketamine product of claim 4, wherein the infusion bag is contained with an overwrap.

126. Biomed is available as a 100 mg per 100 mL IV infusion in a flexible 100 mL IV bag with overwrap. *Id.* at 10. Therefore, it is my opinion that claim 13 of the '153 patent is anticipated.

**F. Dependent Claim 18**

127. Dependent Claim 18 of the '153 patent recites: The ketamine product of claim 1, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

128. As I explained previously, the POSA would understand that “chemically stable” for the purposes of the '153 patent generally equates to having an acceptable shelf life of the product, *i.e.* where there is resistance to degradation in its environment “on a timescale of its expected usefulness.” Biomed teaches to “[s]tore at or below  $25^{\circ}\text{C}$ ” and discloses that the 100 mg per 100 mL IV infusion bag product has a 24-month shelf life. Ex. 1005 at 10. Regarding the relative humidity limitation, a POSA would know that “[w]here no specific directions or limitations are provided in the article’s labeling, articles must be protected from moisture” in “[a] place that does not exceed 40% average relative humidity at  $20^{\circ}$

(68° F) or the equivalent water vapor pressure at other temperatures.” *See* Ex. 1019 at 1-2, 6. Therefore, it is my opinion that claim 18 of the ’153 patent is anticipated because this limitation is present in Biomed.

**G. Dependent Claim 19**

129. Dependent Claim 19 of the ’153 patent recites: The ketamine product of claim 1, wherein the content of the aqueous ketamine solution after accelerated storage at  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $<25\%$  RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $40\% \text{ RH} \pm 5\% \text{ RH}$  is 97% or greater compared to the ketamine content before storage.

130. Biomed inherently discloses a ketamine product wherein the content of the aqueous ketamine solution after accelerated storage at  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $<25\%$  RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $40\% \text{ RH} \pm 5\% \text{ RH}$  is 97% or greater compared to the ketamine content before storage. The ketamine content after this length of time of storage at these conditions is an inherent characteristic that will naturally result from storing the formulation at these conditions. The patent itself confirms this conclusion. Table 6 of the ’153 patent found that at the claimed conditions for accelerated storage, the same formulation as the 100 mg per 100 mL Biomed formulation (ketamine hydrochloride, sodium

chloride (isotonic) and water for injection, pH between 3.5-5.5 (compare '153 patent Tables 1 and 5 and Ex. 1005 at 1, 10)), had assay amounts of 100.5%, 101.7% and 100.6%. '153 patent, Table 6. Therefore, it is my opinion that claim 19 of the '153 patent is anticipated because this limitation is inherently present in Biomed.

**H. Dependent Claim 20**

131. Dependent Claim 20 of the '153 patent recites: A method of treating a subject in need of analgesia, comprising administering the ketamine product of claim 1 to the subject as a continuous infusion.

132. Biomed is indicated for the “induction of anesthesia” or as the “sole anaesthetic agent.” Ex. 1005 at 1; *see also id.* at 8 (“Ketamine is a rapid-acting, general anaesthetic producing an anaesthetic state characterized by profound analgesia.”). Biomed is administered as a continuous infusion. *Id.* at 2 (“It is recommended that ketamine infusion be administered slowly (over a period of 60 seconds).”). Therefore it is my opinion that claim 20 of the '153 patent is anticipated because this limitation is present in Biomed.

**X. GROUND 2: CLAIMS 1, 2, 4, 6–17, AND 21–23 WOULD HAVE BEEN OBVIOUS**

133. It is my opinion that claims 1, 2, 4, 6–17, and 21–23 would have been obvious in view of the prior art: Biomed (Ex. 1005), Remington 2021 (Ex. 1006), the patent-admitted commercially available infusion bags (exemplified by Ex. 1007, Ex. 1008 and Ex. 1009) and the knowledge of the POSA. The POSA would have

been motivated to combine the teachings of a pre-mixed, not requiring dilution for administration, *i.e.* “ready-to-use,” formulation of ketamine with bags in the prior art that could withstand terminal sterilization or be aseptically filled, for the product to be injected directly to the patient. To the extent the bags could not be terminally sterilized, the POSA would have been motivated to undertake aseptic procedures to ensure the sterility of the final product such that it could be administered directly to the patient. The POSA would have had a reasonable expectation of success in achieving this product, with the claimed shelf life and meeting the claimed stability parameters, as Biomed infusion bags have a shelf life of 24 months, the chemical composition would be stable under long term storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 40\% \pm 5\% \text{RH}$  for twelve months, including as to the ketamine content, and the POSA would expect commercially available bags to withstand terminal sterilization such that the shelf life would not decrease once the bags were either aseptically filled or terminally sterilized.

134. I set forth the teachings of Biomed above at Section IX, and incorporate them herein by reference. In short, here, the Biomed product is available in an infusion bag which contains 100 mg/100 mL (1 mg/mL) ketamine with a shelf life of 24 months from the date of manufacture. It contains only ketamine, sodium chloride, and water for injection, at a pH of 3.5 to 5.5, and it is an isotonic solution for infusion. The POSA would recognize that Biomed was sterile, because, as

described, *e.g.*, in Remington 2021 (Ex. 1006), industry practice required injectable products to be sterile.

135. In addition to being industry practice, national guidelines would require Biomed to be sterile. As explained above, Biomed is a product approved for sale in New Zealand, meaning that it would follow the European Pharmacopoeia for applicable guidance and monographs. Ph. Eur. 2.6.1 specifies that parenteral products would need to be tested for sterility to confirm that the product complies with the European Pharmacopoeia. Ex. 1018 at 158.

136. Remington 2021, a well-known treatise to pharmaceutical formulators, would disclose to the POSA that a sterile product could be manufactured through two mechanisms, filtration and sterilization. Ex. 1006 at 587-88 (Table 29.4). The POSA would know, as confirmed by Remington 2021, that products adversely affected by the heat of thermal sterilization should be filtered through bacteria-retaining filters, followed by aseptic operations to prevent reintroduction of contaminants. *Id.* Consequently, Remington 2021 teaches, and the POSA would understand, that should the product require filtration, “aseptic filling” must follow. *Id.* at 595.<sup>2</sup>

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<sup>2</sup> The 2019 Sterilization Guideline issued by the European Medicines Agency (Ex. 1020) confirms that the understanding in New Zealand, including as it relates to the Biomed product, is consistent with the disclosures of Remington 2021 (Ex. 1006), characterizing the relationship of aseptic processing and sterile filtration as

137. The POSA would be motivated to combine Biomed with the patent-admitted commercially available infusion bags. Biomed is indicated as the sole anaesthetic agent, and/or for the induction of anaesthesia prior to the administration of other general anaesthetic agents, which is administered directly to the patient without prior manipulation required. Ex. 1005 at 2, 10. The POSA would recognize that for treating a patient it would be advantageous to have a direct-to-patient formulation, such as Biomed (*see* Ex. 1005 at 10, 6.5 Nature and contents of container, “Ketamine 100 mg per 100 mL IV Infusion is available in flexible 100 mL IV bag with overwrap”), that would avoid the potential for contamination and dosing and administration errors. While Biomed does not specify the 100 mL IV bag with overwrap used, the POSA would be aware that ketamine was used as an analgesic for infusion treatments and would consider having a suitable infusion bag that would be sufficient to serve that same purpose of administering directly to the patient.

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“closely related and difficult to consider separately, since sterile filtration in most cases is followed by at least one aseptic processing step such as filling.” Ex. 2020 at 4; *see also id.* (even conflating them for some sections). Thus, the POSA would understand that, starting with the Biomed product, even the relevant guidelines would counsel the same course of action for manufacturing an injectable product.

138. A POSA would understand that a suitable infusion bag<sup>3</sup> would require that the ketamine formulation is not contaminated or negatively impacted by the composition of components of the bag. The POSA also would understand that the infusion bag would need to be terminally sterilized or aseptically filled to ensure a sterile drug product for the patient, and that commercially available infusion bags were suitable for this purpose. Ex. 1018 at 158; Ex. 1020 at 4-5, 19; Ex. 1006 at 587-88, 595, 597; *see generally* Ex. 1009; Ex. 1007; Ex. 1008.

139. The specification admits that there were many commercially available infusion bags and films available in the prior art, including numerous options from Hosokawa, SealedAir Corporation (Nexcel brand), etc. Indeed, a POSA reading the specification would understand that the inventors did not invent a novel infusion bag, but rather merely listed suitable commercially available bags.

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<sup>3</sup> Where I reference infusion or intravenous “bags” I also include the films that make up the bags in that discussion.

In one aspect, the intravenous bag is made up of multi-layer polypropylene styrene-block copolymer. Such containers are available commercially under the APP-series film IV bag products manufactured by Polycine, such as APP-114S. In one aspect, the intravenous bag comprises an inner layer made up of a cycloolefin polymer, a middle layer made up of linear low density polyethylene polymer and an outer layer made up of low density polyethylene polymer. Such containers are available commercially available as Polyelite EHC® film bags manufactured by Hosokawa. In another aspect, intravenous bag is made up of an outer layer of polypropylene polymer with styrene-ethylene-butylene (SEB) block copolymer and a middle and inner layer made up of polypropylene based polyolefin polymer with styrene-ethylene butylene block copolymer. Such containers are available commercially under the brand name Inerta 103 and are manufactured by Technoflex. In another aspect, the intravenous bag is made up of multilayer polyolefin film. Such containers are available as Nexcel brand M312 and M312A® films by SealedAir Corporation, and as M312 films from other manufacturers. Other commercially-available intravenous bags that are stable, with low leachables, and without physical deformation during terminal sterilization are also contemplated in this disclosure. In one aspect, the infusion bag comprises a single layer of flexible film.

In one aspect, the infusion bag comprises a flexible film. In some aspects, the flexible film may be a multilayer film or a single layer film. In some aspects, the innermost layer of the infusion container is made-up of a material that shows 45 minimal or no adsorption of ketamine thereby causing no loss of potency and/or assay percentage during preparation, sterilization and during storage. In some aspects, the multilayer film may comprise other layers that may be made up of materials such as polyethylene, polypropylene, modified 50 polyolefin-polyethylene polymers, styrene-polyolefin based polymers and block co-polymers thereof, etc. In certain aspects, the infusion bag comprises a flexible multilayer film comprising polyolefin and styrene-ethylene-butylene (SEB) block copolymer. In certain aspects, the infusion bag comprises 55 a multilayer polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises 2 to 5 layers of polypropylene styrene-block copolymer based film. In certain aspects, the infusion bag comprises a 3-layer 60 polypropylene styrene-block copolymer based film. In one aspect, the infusion bag comprises a flexible multilayer film comprising a multilayer polyolefin film. In some aspects the infusion bag comprises 2 to 7 layers of polyolefin film. In some aspects, the infusion bag comprises a 5 layer polyolefin film. In some aspects, the flexible film may be a 65 multilayer film or a single layer film. In some aspects, the film may be an M312 film, such as Nexcel brand M312A

film manufactured by SealedAir Corporation; an M315 film  
manufactured by SealedAir Corporation; an APP-series film  
manufactured by Polycine, such as APP-114S film manu-  
factured by Polycine; a polypropylene film, such as those  
5 manufactured by Technoflex, such as an Inerta® film manu-  
factured by Technoflex; a cycloolefin polymer with a middle  
layer made up of linear low density polyethylene polymer  
and an outer layer made up of low density polyethylene  
polymer, such as those manufactured by Hosokawa; an  
10 Inerta 103 film, made up of an outer layer of polypropylene  
polymer with styrene-ethylene-butylene (SEB) block copo-  
lymer and a middle and inner layer made up of polypropyl-  
ene based polyolefin polymer with styrene-ethylene buty-  
lene block copolymer, which may be manufactured by  
15 Technoflex; or another commercially-available polymer film  
designed for use in intravenous bag products. In certain  
aspects, other polymers that are stable, with low leachables,  
and without physical deformation during terminal steriliza-  
tion may also be used for the infusion bag.

Ex. 1001 at 8:17-41, 9:42-10:19.

140. As the patent admits, the commercially available bags in the prior art had the properties of the claims, including the material and layers. The ports and material of the ports would have been readily ascertainable to the POSA from viewing and assessing these commercially available bags.

141. Commercial literature describes the numerous films and bag products listed in the patent. For example, SealedAir Nexcel's M312 and M315 films are described in datasheets, describing the multi-layered, polyolefin-based extrusion film, and its use for medical and pharmaceutical applications. *See* Ex. 1007 at 1-2; Ex. 1008 at 1-2. Technoflex Inerta describes Inerta® bags as single or multi-tubular,

aseptically filled polypropylene bags, with a twist off on one port, which are placed in double packaging. Ex. 1009 at 6.

142. The patent-admitted commercially available infusion bags satisfy the limitations of claims 6–12 and 14 as the applicant confirmed they were suitable for use in the invention. *See* Ex. 1001 at 8:17-41, 9:42-10:19. All of the commercially available products listed would be expected to have at least one port, and as disclosed in the patent and confirmed in the M312 Film Data Sheet, M315 Film Data Sheet, and Technoflex Inerta, the film or bag is multilayer (including up to 5 layers) and polyolefin-based. *See* Ex. 1007 at 2 (describing a 5-layer polyolefin-based extrusion film); Ex. 1008 at 2 (describing a 4-layer, polyolefin-based extrusion film); Ex. 1009 at 6 (stating that Inerta bags are polypropylene sterile bags).

143. Technoflex Inerta includes an image of the Inerta® IV drug delivery bag which depicts two ports, one with a twist-off, and one welded shut. Ex. 1009 at 6. The twist-off closure forms two chambers, one in contact with the formulation, and one forming an air chamber.

144. For the reasons set forth below, a POSA would regard the combination of the claimed bags and films with the Biomed pre-mixed formulation as obvious to provide a sterile ketamine solution administrable directly to patients.

**A. Independent Claim 1**

145. I have reproduced independent claim 1 of the '153 patent above, which states: A ketamine product comprising an aqueous solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection, wherein the ketamine solution is preservative-free and anti-microbial free, wherein the ketamine product is sterile and ready-to-use (RTU), wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5, and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C. To the extent it is not considered anticipated, independent claim 1 is invalid as obvious for generally the same reasons as set forth above that this claim would be anticipated as fully disclosed by Biomed, and I incorporate my analysis at paragraphs 111-116 herein. Based on an analysis of the scope and content of the prior art and a comparison of the prior art to the patent claim in light of the level of ordinary skill in the art, a POSA would find any differences between the prior art and the claim insubstantial and any necessary modification of the prior art to achieve the limitations of claim 1 would be well within the ordinary skill, and a POSA would have more than a reasonable expectation of success in achieving the limitations of claim 1.

**B. Dependent Claim 2**

146. Dependent Claim 2 of the '153 patent recites: The ketamine product of claim 1, wherein the ketamine product has been terminally sterilized.

147. As stated above at paragraph 114, the POSA would recognize that as an approved product for intravenous administration, Biomed would have needed to be sterile. A POSA also would recognize that sterilization could be accomplished either by terminal sterilization or through the use of aseptic filling methods, as disclosed in Remington 2021 and confirmed by relevant guidelines. Ex. 1018 at 158; Ex. 2020 at 4-5, 19; Ex. 1006 at 587-88, 595, 597. Therefore, it is my opinion that claim 2 of the '153 patent is invalid as obvious.

**C. Dependent Claim 4**

148. I have reproduced independent claim 4 of the '153 patent above, which states: The ketamine product of claim 1, wherein the aqueous ketamine solution is contained in an infusion bag comprising at least one port sealed with a closure. To the extent it is not considered anticipated, claim 4 is invalid as obvious for generally the same reasons as set forth above that this claim would be anticipated as fully disclosed by Biomed, and I incorporate my analysis at paragraphs 120-121 herein. Based on an analysis of the scope and content of the prior art and a comparison of the prior art to the patent claim in light of the level of ordinary skill in the art, a POSA would find any differences between the prior art and the claim insubstantial

and any necessary modification of the prior art to achieve the limitations of claim 4 would be well within the ordinary skill, and a POSA would have more than a reasonable expectation of success in achieving the limitations of claim 4.

**D. Dependent Claim 13**

149. I have reproduced dependent claim 13 of the '153 patent above, which states: The ketamine product of claim 4, wherein the infusion bag is contained within an overwrap. To the extent it is not considered anticipated, claim 13 is invalid as obvious for generally the same reasons as set forth above that this claim would be anticipated as fully disclosed by Biomed, and I incorporate my analysis at paragraphs 125-126 herein. Based on an analysis of the scope and content of the prior art and a comparison of the prior art to the patent claim in light of the level of ordinary skill in the art, a POSA would find any differences between the prior art and the claim insubstantial and any necessary modification of the prior art to achieve the limitations of claim 13 would be well within the ordinary skill, and a POSA would have more than a reasonable expectation of success in achieving the limitations of claim 13.

**E. Dependent Claims 6–12 and 14**

150. Claims 6–12 and 14 describe the properties of the infusion bag of claim 4. They are recited below:

Claim 6: The ketamine product of claim 4, wherein the at least one port comprises a multilayer polyolefin and styrene block copolymer tube material.

Claim 7: The ketamine product of claim 4, wherein the closure comprises a plastic material.

Claim 8: The ketamine product of claim 4, wherein the closure is a twist-off closure and comprises a membrane that creates a barrier, splitting the twist-off closure in two parts, wherein a first of the two parts is an inferior part of the membrane that is in direct contact with the ketamine solution, and the second of the two parts is a superior part of the membrane that is in contact with a zone that forms an air chamber into the closure.

Claim 9: The ketamine product of claim 7, wherein the closure is a twist-off closure that comprises polypropylene (PP), low density polyethylene (LDPE), polyolefin block copolymer, or any combination thereof.

Claim 10: The ketamine product of claim 4, wherein the infusion bag comprises a flexible multilayer film comprising a polymer selected from the group consisting of polyethylene, polypropylene, modified polyolefin-polyethylene polymers, styrene-polyolefin based polymers, block copolymers, and a combination thereof.

Claim 11: The ketamine product of claim 4, wherein the infusion bag comprises a flexible multilayer film comprising 2 to 5 layers, wherein at least one layer comprises polypropylene styrene-block copolymer.

Claim 12: The ketamine product of claim 4, wherein the infusion bag comprises a 3-layer film wherein at least one layer comprises polypropylene styrene-block copolymer.

Claim 14: The ketamine product of claim 13, wherein the overwrap comprises four layers comprising polyester, aluminum, polypropylene, and polyester.

151. Claims 6–12 and 14 would have been obvious over Biomed in view of the prior art, *i.e.*, the commercially available bags, films, and overwraps described

above. The POSA would understand from reading the specification that the inventors did not invent a novel infusion bag and that multiple commercially available bags had the materials and configurations that are set forth in the claims. The POSA would have been motivated to use commercially available infusion bags for the purpose of administering a sterile infusion product to a patient. Therefore, it is my opinion that claims 6–12 and 14 of the '153 patent are invalid as obvious.

152. The commercial literature, including M312 Film, M315 Film, and Technoflex Inerta confirm the availability of the bags disclosed in the patent prior to the effective filing date, and the relevant properties: constructed of polypropylene, and encompassing multi-film designs. This is set forth further above.

**F. Dependent Claim 15**

153. Dependent claim 15 of the '153 patent recites: The ketamine product of claim 1, wherein the ketamine product has been autoclaved.

154. Dependent claim 15 would have been obvious over Biomed and additional prior art discussed as follows. Remington 2021 describes acceptable methods of manufacturing for injectable products, including by aseptic filtration and terminal sterilization. The POSA would understand that terminal sterilization takes many forms, which include the use of heat or steam sterilization in order to sterilize a drug product. Ex. 1018 at 158; Ex. 1020 at 4-5, 19; Ex. 1006 at 587-88, 595, 597. The POSA would further know that this would take place in an autoclave, and would

be motivated to use this technique in order to ensure a sterile drug product with a suitable shelf life, and with the knowledge that the infusion bags available could be subjected to terminal sterilization without affecting the drug product. Therefore it is my opinion that claim 15 of the '153 patent is invalid as obvious.

**G. Independent Claim 16**

- 1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection,**

155. These limitations are disclosed in Biomed for the same reasons as set forth for these limitations of claim 1, above at paragraphs 111-112. I incorporate my opinion for claim 1 herein.

- 2. wherein the ketamine solution is preservative-free and anti-microbial free,**

156. These limitations are disclosed in Biomed for the same reasons as set forth for these limitations of claim 1, above at paragraph 113. I incorporate my opinion for claim 1 herein.

- 3. wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5,**

157. This limitation is disclosed in Biomed for the same reasons set forth for this limitation of claim 1, above at paragraph 115. I incorporate my opinion for claim 1 herein.

**4. and wherein the ketamine solution is contained in a terminally sterilized, ready-to-use infusion container,**

158. The “terminally sterilized” limitation is obvious for the same reasons as set forth for the corresponding limitation of claim 2, above at 146. As stated above, the POSA would recognize that as an approved product for intravenous administration, Biomed would have needed to be sterile, and this could be accomplished either by terminal sterilization or using aseptic filling methods. Ex. 1018 at 158; Ex. 2020 at 4-5, 19; Ex. 1006 at 587-88, 595, 597. I incorporate my opinions for claims 1 and 2 herein. The “ready-to-use” limitation is disclosed in Biomed for the same reasons set forth for this limitation of claim 1, above at paragraph 114. I incorporate my opinion for claims 1 and 2 herein.

**5. and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C.**

159. This limitation is disclosed in Biomed for the same reasons as set forth for this limitation of claim 1, above at paragraph 116. I incorporate my opinion for claim 1 herein.

**6. Conclusion**

160. Based on the foregoing, it is my opinion that claim 16 of the '153 patent is obvious.

**H. Dependent Claim 17**

161. Dependent Claim 17 of the '153 patent recites: The ketamine product of claim 16, wherein the tonicity adjustment agent comprises sodium chloride, dextrose, glycerin, mannitol, potassium chloride, or any combination thereof.

162. Biomed contains sodium chloride and is an isotonic solution for infusion. Ex. 1005. at 1, 10. The '153 patent discloses that sodium chloride is a tonicity adjusting agent (see, e.g., '153 patent at 3:8-10), consistent with the disclosure of Remington 1995 (“[t]he first two of these methods [of adjusting tonicity] can be used with a three step problem solving process based on sodium chloride.”). Remington 1995 at 620-21. Therefore, it is my opinion that claim 17 of the '153 patent is obvious.

**I. Independent Claim 21**

- 1. A ketamine product comprising an aqueous ketamine solution comprising about 0.5 to about 2.5 mg/mL ketamine, a tonicity adjusting agent, and water for injection,**

163. These limitations are disclosed in Biomed for the same reasons as set forth for these limitations of claim 1, above at paragraphs 111-112. I incorporate my opinion for claim 1 herein.

**2. wherein the ketamine solution is preservative-free and anti-microbial free,**

164. These limitations are disclosed in Biomed for the same reasons as set forth for these limitations of claim 1, above at paragraph 113. I incorporate my opinion for claim 1 herein.

**3. wherein the pH of the aqueous ketamine solution is about 3.5 to about 5.5,**

165. This limitation is disclosed in Biomed for the same reasons set forth for this limitation of claim 1, above at paragraph 115. I incorporate my opinion for claim 1 herein.

**4. wherein the ketamine solution is contained in an infusion bag,**

166. This limitation is disclosed in Biomed for the same reasons set forth for claim 4, above at paragraph 121. I incorporate my opinion for claim 1 herein.

**5. wherein the ketamine product has been aseptically filled,**

167. This limitation would have been obvious over Biomed and additional prior art discussed as follows. As stated above at paragraph 114, the POSA would recognize that as an approved product for intravenous administration, Biomed would have needed to be sterile. A POSA also would recognize that sterilization could be accomplished either by terminal sterilization or using aseptic filling methods. Ex. 1018 at 158; Ex. 1020 at 4-5, 19; Ex. 1006 at 587-88, 595, 597. Therefore, the POSA

would have regarded these standard procedures as an obvious choice for manufacturing a sterile product.

**6. and wherein the ketamine product is sterile and ready-to-use (RTU),**

168. This limitation is disclosed in Biomed for the same reasons set forth for this limitation of claim 1, above at paragraph 114. I incorporate my opinion for claim 1 herein.

**7. and wherein the ketamine product has a shelf-life of more than six months when stored at a controlled room temperature between 15-30°C.**

169. This limitation is disclosed in Biomed for the same reasons as set forth for this limitation of claim 1, above at paragraph 116. I incorporate my opinion for claim 1 herein.

**8. Conclusion**

170. Based on the foregoing, it is my opinion that claim 21 of the '153 patent is invalid as obvious.

**J. Dependent Claim 22**

171. Dependent Claim 22 of the '153 patent recites: The ketamine product of claim 16, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

172. This limitation is disclosed in Biomed for the same reasons as set forth for this limitation of claim 18, above at paragraph 128. I incorporate my opinion for claim 18 herein.

**K. Dependent Claim 23**

173. Dependent Claim 23 of the '153 patent recites: The ketamine product of claim 21, wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

174. Biomed is a ketamine product wherein the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$  for the same reasons as set forth for this limitation of claim 18, above at paragraph 128. I incorporate my opinion for claim 18 herein. Therefore the POSA would have known and expected that the ketamine product would be chemically stable following 24 months of storage at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  with relative humidity (RH) at  $40\% \pm 5\%$ .

**XI. NO SECONDARY CONSIDERATIONS**

175. The applicant argued during prosecution that the secondary considerations of teaching away and unexpected results supported the nonobviousness of the alleged invention. I disagree.

176. I see no evidence of teaching away in the prior art. The applicant's basis for this claim was that "the prior art specifically teaches away from storing a diluted ketamine solution in room temperature for prolonged periods (e.g., at least six months as required by all pending claims or twenty-four months as recited in dependent claims 23, 31, and 32)" because the concentrated ketamine, once diluted, required immediate use and disposal. Ex. 1002 at 244. But this argument does not take into account the Biomed product available in New Zealand, which teaches a ketamine solution within the scope of the claims that is stored at room temperature for 24 months. Ex. 1005 at 10. Particularly for this reason, applicant's argument fails.

177. Applicant further argued that the extended stability in a ketamine formulation without a preservative was unexpected over the concentrated products available in the prior art. This also does not take into account the Biomed product available in New Zealand, which teaches a ketamine solution within the scope of the claims that has extended stability. I understand that to show unexpected results, the applicant must make the comparison between the claimed invention and the closest prior art, an analysis not undertaken by the applicant because the closest prior art would be the other ready-to-use ketamine product available, not concentrated products. This is at least because (1) concentrated products required manipulation, unlike Biomed in a ready-to-use similar presentation to the claims, and (2) following

manipulation, use in a short time period before requiring disposal, unlike Biomed, which was aligned with the longer room temperature stability of the claims.

178. Even if the proper analysis had been undertaken, unexpected results were not shown. The applicant alleged that the unexpected results were “extended stability” achieved “without a preservative.” The “extended stability” could refer to the claimed “shelf-life of more than six months when stored at a controlled room temperature between 15-30°C” (claims 1, 16, 21), “the ketamine or a pharmaceutically acceptable salt thereof is chemically stable following 24 months of storage at 25°C ± 2°C with relative humidity (RH) at 40%±5%” (claims 18, 22-23), and/or “the ketamine content of the aqueous ketamine solution after accelerated storage at 40°C ±2°C/<25% RH for 6 months is greater than 97%; and/or wherein the ketamine content of the aqueous ketamine solution after long-term storage for 12 months at 25°C ±2°C/40% RH ±5% RH is 97% or greater compared to the ketamine content before storage” (claim 19). This is not a superior benefit over Biomed, and is a mere difference in degree, not in kind. The ketamine 100 mg per 100 mL IV infusion bag presentation of Biomed had a shelf life of 24 months (Ex. 1005 at 10) without any preservative in the formulation (*id.* at 2). Therefore, there are no unexpected results which would justify nonobviousness of the claims of the ’153 patent.

Executed on March 20, 2026.

  
Michael B. Maurin, R.Ph., Ph.D.