

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,
Petitioner,

v.

SEIKAGAKU CORPORATION,
Patent Owner.

Case No. IPR2025-00440
Patent No. 11,236,318

**PETITIONER'S OPPOSITION TO
PATENT OWNER'S CONTINGENT MOTION TO AMEND**

TABLE OF CONTENTS

I.	INTRODUCTION	1
A.	THE PROPOSED AMENDMENTS ENLARGE CLAIM SCOPE	1
B.	AMENDED CLAIM 22 WOULD STILL HAVE BEEN OBVIOUS OVER THE PRIOR ART OF THE INSTITUTED GROUNDS.....	6
1.	Person of Ordinary Skill in the Art (“POSA”).....	7
2.	PO’s Motion Improperly Relies On Expert Testimony From Experts Who Were Unaware of Claim 22.....	7
3.	Claim 22 Finds Even Less Support Or Enabling Disclosure From The ’767 Application Than Original Claim 21	8
a.	If the Claim Requires The Factor C To Have the Claimed Residual Activity In Each of Two Separate Ionic Solutions, There Is No Written Description Support For The Full Scope of Claim 22’s Requirement That <i>Limulus</i> <i>polyphemus</i> Factor C Be Higher Than Factor C From Sf9 or Native.....	8
b.	Proposed Claim 22 is Not Described In the ’767 Application.....	9
c.	Even With The Hindsight Benefit of the Known <i>Limulus</i> <i>polyphemus</i> Factor C Sequence, Differences In Sequence Were Apparent.	13
d.	“Functional Interchangeability” Of Native Proteins Is Not Predictive of Residual Activity in Recombinant Proteins	15
e.	If The Ionic Concentrations Must Be In the Same Solution, Claim 22 is Not Described	21
f.	The Experimentation Required To Practice Claim 22’s Full Scope Is Undue.....	22
4.	There is No Evidence of Secondary Considerations That Would Render Claim 22 Non-Obvious As of April 30, 2019.	23
C.	THE PROPOSED AMENDMENTS RENDER CLAIM 22 INDEFINITE.....	24
II.	CONCLUSION.....	25

TABLE OF AUTHORITIES

CASES

<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015)	10
<i>Ariad Pharm., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (<i>en banc</i>).....	13, 15, 21
<i>Boston Scientific Corp. v. Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011)	14
<i>Brita LP v. Int’l Trade Comm’n</i> , 156 F.4th 1326 (Fed. Cir. 2025)	12
<i>Cuozzo Speed Techs., LLC v. Lee</i> , 579 U.S. 261 (2016)	24
<i>Cuozzo Speed Techs., LLC</i> , 793 F.3d 1268 (Fed. Cir. 2015)	2
<i>Epistar Corp. v. Lowes Cos., Inc.</i> , 2020 WL 771096 (C.D. Cal. Feb. 11, 2020)	23
<i>In re Kuenzel</i> , Appeal 2009-015373, 2011 WL 938717, (B.P.A.I. Mar. 17, 2011)	21
<i>Lockwood v. Am. Airlines, Inc.</i> , 107 F.3d 1565 (Fed. Cir. 1997)	9, 21
<i>MagSil Corp. v. Hitachi Glob. Storage Inc.</i> , 687 F.3d 1377 (Fed. Cir. 2012)	23
<i>Nautilus, Inc. v. Biosig Instruments, Inc.</i> , 572 U.S. 898 (2014)	24, 25
<i>Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC</i> , 584 U.S. 325 (2018)	25
<i>In re Packard</i> , 751 F.3d 1307 (Fed. Cir. 2014)	24, 25

<i>Regents of the Univ. of Minn. v. LSI</i> , 926 F.3d 1327 (Fed. Cir. 2019)	24
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<i>Application Rogoff</i> , 261 F.2d 601 (C.C.P.A. 1958)	3
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STATUTES

35 U.S.C. § 112	1, 12, 13, 21
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35 U.S.C. § 120	9
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35 U.S.C. § 316(d)(3)	1
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REGULATIONS

37 C.F.R. § 42.121(a)(2)(ii)	1
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LISTING OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,236,318 (“the ’318 patent”)
1002	Declaration of Siddhartha Jain, Ph.D., PMP (“Jain”)
1003	Curriculum Vitae of Dr. Siddhartha Jain, Ph.D., PMP
1004	Prosecution History for U.S. Application No. 16/399,386
1005	International Patent Publication No. WO 2018/074498 A1
1006	U.S. Patent Application No. 14/650,767, as filed June 9, 2015
1007	Muta et al., “Limulus Factor C. An endotoxin-sensitive serine protease zymogen with a mosaic structure of complement-like, epidermal growth factor-like, and lectin-like domains,” <i>J Biol Chem.</i> 1991 Apr 5; 266(10):6554-61.
1008	Gan et al., “Analysis of Protein Sequence/Structure Similarity Relationships,” <i>Biophys J.</i> 2002 Nov; 83(5):2781-91.
1009	U.S. Patent Application Publication No. 2015/0307864
1010	Karen McClymont, Ph.D. Thesis, submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy from the University of Glasgow, Institute of Molecular, Cell and Systems Biology College of Medical, Veterinary and Life Sciences, March 2017.
1011	Transition Certification for U.S. Patent Application No. 15/983,725, filed May 31, 2019.
1012	U.S. Patent No. 5,716,834
1013	Declaration of Dr. Mary K. Bolin
1014	U.S. Patent No. 5,858,706
1015	International Patent Publication No. WO 2000/026366 A1
1016	Iwanaga, Sadaaki, “Biochemical principle of <i>Limulus</i> test for detecting bacterial endotoxins,” <i>Proc. Jpn. Acad., Ser. B. Phys Biol Sci.</i> 2007 May; 83(4):110-9.
1017	RESERVED
1018	RESERVED
1019	Japanese Priority Document JP2012-269840 (certified translation, plus original)
1020	U.S. Application No. 14/650,767, addition to PCT specification
1021	Higdon, R. et al., “Modeling sequence and function similarity between proteins for protein functional annotation,” <i>Proc Int Symp High Perform Distrib Comput</i> ; 2010: 499–502.

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1022	Tokunaga, F., et al. "Further studies on lipopolysaccharide-sensitive serine protease zymogen (Factor C): Its isolation from <i>Limulus polyphemus</i> hemocytes and identification as an intracellular zymogen activated by α -chymotrypsin, not by trypsin," <i>J. Biochem.</i> 1991 Jan; 109(1):150-7.
1023	Levin, J., Bang, F., "The role of endotoxin in the extracellular coagulation of <i>Limulus</i> blood," <i>Bulletin of John's Hopkins Hospital.</i> 1964 Sep: 115:265-74.
1024	Walls, E. et al, The Horseshoe Crab, <i>Limulus polyphemus</i> : 200 Million Years of Existence, 100 Years of Study, <i>Reviews in Fisheries Science.</i> 2002; 10(1):39-73.
1025	Carmichael, R., et al., "Changing Global Perspectives on Horseshoe Crab Biology, Conservation, and Management," Springer, Ch. 29: "Biotechnology Efforts to Conserve Horseshoe Crabs Through the Development of Recombinant Factor C-Based Endotoxin Test" pp. 501-512 (2015).
1026	Dwarakanath et al., "Recombinant COS-1 cells express <i>Carcinoscorpius rotundicauda</i> Factor C," <i>Biotechnology Letters.</i> 1997 April; 19(4):357-361.
1027	Wang, J. et al., "Functional expression of full length <i>Limulus</i> Factor C in stably transformed Sf9 cells," <i>Biotechnology Letters.</i> 2001; 23:71-76.
1028	Ding et al, "A new era in pyrogen testing," <i>Trends in Biotechnology.</i> 2001 Aug; 19(8):277-81.
1029	U.S. Appln. No.: 14/650,767, "Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin," Declaration Under 37 C.F.R. § 1.132, Feb. 22, 2018.
1030	Barrabes, S. et al., "Effect of sialic acid content on glycoprotein p/ analyzed by two-dimensional electrophoresis," <i>Electrophoresis.</i> 2010 Sep; 31(17):2903-12.
1031	Palomares, L.A., "Production of Recombinant Proteins: Challenges and Solutions," From: <i>Methods in Molecular Biology</i> , vol. 267: <i>Recombinant Gene Expression: Reviews and Protocols</i> , Second Edition Edited by: P. Balbás and A. Lorence © 2004 Humana Press Inc., Totowa, NJ, pp. 15-51
1032	U.S. Patent No. 6,645,724
1033	Mizumura, H., et al., "Genetic engineering approach to develop next-generation reagents for endotoxin quantification," <i>Innate Immunity.</i> 2017 Feb; 23(2):136-146.

Exhibit	Description
1034	Ding et al., “Expression of full length and deletion homologues of <i>Carcinoscorpius rotundicauda</i> Factor C in <i>Saccharomyces cerevisiae</i> : immunoreactivity and endotoxin binding,” <i>Journal of Endotoxin Research</i> . 1997; 4(1): 33-43.
1035	International Patent Publication No. WO 2014/092079 A1 (“the ‘082 PCT”)
1036	Wang et al., “Modular Arrangement and Secretion of a Multidomain Serine Protease,” <i>J Biol Chem</i> . 2002 Sep 27; 277(39):36363-72.
1037	Marengo-Rowe, Alain, J., “Structure-function relations of human hemoglobins,” <i>Proc (Bayl Univ Med Cent)</i> 2006 Jul; 19(3):239–245.
1038	Sekiguchi, K. and Shuster, C.N., “Limits on the Global Distribution of Horseshoe Crabs (Limulacea): Lessons Learned from Two Lifetimes of Observations: Asia and America,” <i>Biology and Conservation of Horseshoe Crabs</i> , 2009.
1039	Hossler et al., “Optimal and consistent protein glycosylation in mammalian cell culture,” <i>Glycobiology</i> . 2009 Sep; 19(9):936-4.
1040	RESERVED
1041	RESERVED
1042	U.S. Appln. No.: 17/554,128, “Novel Recombinant Factor C And Method for Producing the Same, and Method for Measuring Endotoxin” Non-Final Office Action, Mar. 20, 2025 (“‘128 App. NFR”)
1043	European Patent No. 3530670, “Method for producing endotoxin detecting agent comprising recombinant limulus factor c and use thereof,” Response to Opposition, May 9, 2025
1044	European Patent No. 3441466, “Method for Producing a Novel Recombinant Factor C, Method for Mitigating Reaction Inhibition In Endotoxin Assays, And Method for Measuring Endotoxin,” Decision on Opposition, Oct. 26, 2022
1045	USP, General Chapter Prospectus: Use of Recombinant Reagents in Bacterial Endotoxins Test. May 29, 2020
1046	Stewart, C.M., “Interim Processes for PTAB Workload Management,” Memorandum dated March 26, 2025
1047	U.S. Appln. No.: 17/554,128, “Novel Recombinant Factor C And Method for Producing the Same, and Method for Measuring Endotoxin” Amendment under 37 C.F.R. § 1.111 , Jan. 28, 2025
1048	European Patent No. 3530670, “Method for producing endotoxin detecting agent comprising recombinant limulus factor c and use thereof,” Notice of Opposition, Nov. 22, 2024

Exhibit	Description
1049	RESERVED
1050	U.S. Appln. No.: 16/331,810, “Recombinant Proteins Derived From Genus <i>Limulus</i> , and DNA Molecules Encoding Same,” Notice of Abandonment, Mar. 14, 2023
1051	Press Release, “USP Provides Guidance on the Use of Recombinant Reagents for the Bacterial Endotoxin Test” May 29, 2020
1052	U.S. Patent Application Publication No. 2019/0241629 (“629 publication”)
1053	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Non-Final Office Action, Sept. 16, 2016
1054	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Final Office Action, Apr. 13, 2017
1055	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Amendment under 37 C.F.R. § 1.111 , Mar. 16, 2017
1056	RESERVED
1057	RESERVED
1058	RESERVED
1059	RESERVED
1060	RESERVED
1061	RESERVED
1062	Transcript of August 1, 2025 Conference Call
1063	Email from McKeown, Scott, RE: PGR2025-00023 and IPR2025-00440: Request for Position on Motions to Compel Routine Discovery (Jun. 25, 2025)
1064	Declaration of Chelsea A. Loughran in Support of Admission <i>Pro Hac Vice</i>
1065	Transcript of November 4, 2025 Deposition of Siddhartha Jain, Ph.D., PMP
1066	Huaman et al., “Genomic Serveillance of Rabies Virus in Georgian Canines,” <i>Viruses</i> . 2023 Aug 24;15(9):1797.
1067	Transcript of February 12, 2026 Deposition of Brain Schaefer, Ph.D.
1068	Transcript of February 13, 2026 Deposition of Brain Schaefer, Ph.D.
1069	Transcript of January 28, 2026 Deposition of Tina Morris, Ph.D.
1070	RESERVED
1071	Second Declaration of Siddhartha Jain, Ph.D., PMP

I. INTRODUCTION

Patent Owner's (PO's) Contingent Motion to Amend ("Motion," Paper 27) should be denied for at least three independent and dispositive reasons. First, proposed substitute claim 22 is impermissibly broader than challenged claim 21. Second claim 22 fails to cure the written description and enablement deficiencies of claim 21. To the extent substitute claim 22 is deemed, like claim 21, to lack written description support or an enabling disclosure based on its priority disclosure (U.S. Application No. 14/650,767), claim 22 is equally obvious over the prior art presented in Grounds 1 and 2 of the Petition. Third, claim 22 is facially indefinite under 35 U.S.C. § 112.

Because claim 22 is an improper substitute claim and is unpatentable in any case, the Motion should be denied.

A. THE PROPOSED AMENDMENTS ENLARGE CLAIM SCOPE

A motion to amend may not "enlarge the scope of the claims of the patent." 35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii). Here, the Motion seeks amendments that enlarge the scope of original claim 21 in at least two ways. First, the amendment deletes claim content, including the closed "consisting of" transitional phrase, which by definition opens the claim to additional unrecited elements. Second, the amendment removes the *fixed* lower end of the claimed range for residual activity of recombinant Factor C in each of the recited ionic

solutions and replaces each fixed lower end with a *variable* requirement that such Factor C proteins instead have a residual activity greater than that of the residual activity value of a comparator protein. Even though substitute claim 22 recites a higher residual activity in *both* ionic solutions, the amendment is impermissible in scope because, depending on the residual activity of that comparator protein, the variable requirement allows for recombinant Factor C proteins that would infringe substitute claim 22, where the same proteins would not have infringed original claim 21. Because the proposed amendment vitiates the original fixed lower bound in favor of a comparator protein analysis such that it is no longer limited by the previously claimed bounds, it captures scope that was not previously covered by claim 21, and is impermissible as a matter of law. *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1283 (Fed. Cir. 2015) (“[A] claim is broader in scope than the original claims if it contains within its scope any conceivable apparatus or process which would not have infringed the original patent. The same test applies in...IPRs.”).¹

Original claim 21 requires that the HEK-293 recombinantly produced *L. polyphemus* horseshoe crab Factor C protein “exhibit[] a residual activity of at least one selected from the group consisting of: (1) 10% or higher in the presence of 21 mM sodium citrate; and (2) 15% or higher in the presence of 16 mM

¹ Emphasis added and internal citations omitted unless otherwise noted.

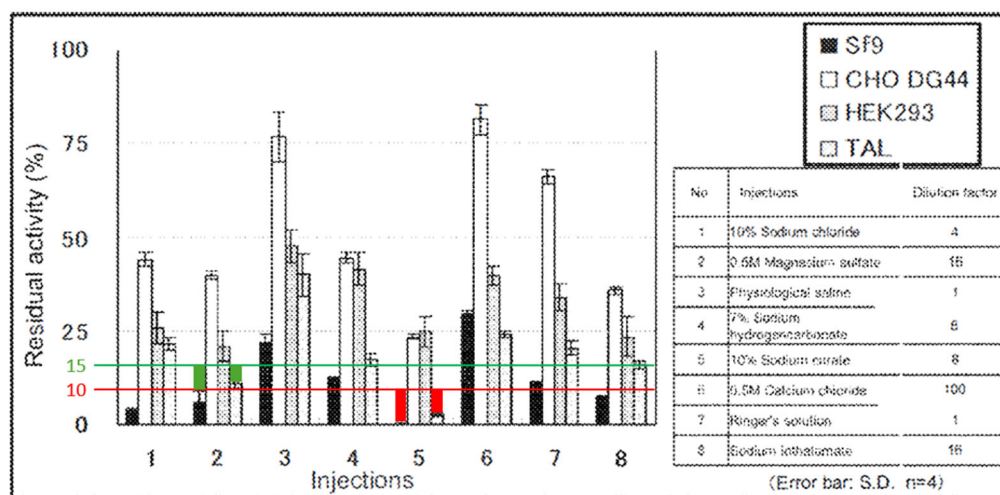
magnesium sulfate.” EX1001, cl. 21. PO’s first amendment replaces the “at least one of” requirement with a requirement instead that the claimed Factor C protein exhibit a particular residual activity “in the presence of 21 mM sodium citrate *and* 16 mM magnesium sulfate.” As discussed in Section I.C. *infra* the use of the word “and” in amended claim 22 renders that claim indefinite. Assuming, however, the residual activity requirement applies to the two claimed ionic solutions separately, PO’s replacement of the “consisting of at least one of” claim language with language requiring a particular residual activity “in the presence of” both 21 mM sodium citrate and 16 mM magnesium does not narrow as PO alleges but amplifies the expansion from “consisting of”. Deletion of this “consisting of” language converts the closed limitation requiring that either of the residual activity requirements is met to an open ended claim that requires the two noted residual activity requirements to be met, *plus any other requirements* as well. *Application of Rogoff*, 261 F.2d 601, 603-04 (C.C.P.A. 1958) (affirming Board finding that certain appealed reissued claims were broadened in scope—“It is well settled that...a claim is broadened if it is broader in any respect than the original claim, even though it may be narrowed in other respects.”).

PO’s second amendment undisputedly serves to broaden claim 21, capturing claim scope previously not covered by that claim. Instead of the claimed fixed 10% (in 21mM sodium citrate) and 15% (in 16 mM magnesium sulfate) lower

range values of claim 21, PO sets the lower range value for residual activity of the claimed recombinant Factor C proteins instead to a floating value of that of the “corresponding *L. polyphemus* Factor C protein expressed in a Sf9 cell or a native *L. polyphemus* Factor C protein.”

The only data provided in the '767 Application is FIG. 7, reproduced below.

[Fig. 7]



Amended claim 22 (like claim 21) recites recombinant Factor C proteins from the *L. polyphemus* horseshoe crabs. However, as discussed extensively in the Petition, the '767 Application provides no examples, data, or disclosure of the claimed recombinant *L. polyphemus* horseshoe crabs across the full scope of the full scope of the residual activity range (a lack of disclosure that forms the basis for Petitioner’s priority argument (Pet. 22-35)). But, considering the data provided in FIG. 7 for the sake of argument (without conceding that it supports claim 21 or claim 22), it is easy to see how proposed claim 22 is broader than claim 21. Based

on the report in Figure 7, the HEK293 recombinantly-produced Factor C proteins in 21 mM sodium citrate (lane 5) exhibit approximate residual activities as follows: Sf9 – 1%, CHO DG44 – 24%, HEK293 – 21%, TAL – 4%

Based on the same Figure 7, the HEK293 recombinantly-produced Factor C proteins in 16 mM magnesium sulfate (lane 2) exhibit residual activities as follows: Sf9 – 5%, CHO DG44 – 35%, HEK293 – 20%, TAL – 10%

In the reported data in Figure 7, the HEK293 results fall within the scope of claim 21 because for lane 5, the residual activity falls above 10%. PO's expert confirmed that a hypothetical Factor C recombinant protein produced in HEK293 exhibiting a residual activity just below this—for example 9%--would be greater than the reported values for Sf9 and native, but would not satisfy the residual activity requirement of claim 21. EX1067, 61:5-63:10. Similarly, in the reported data in Figure 7, the HEK293 results fall within the scope of claim 21 because, in lane 2, the residual activity falls above 15%. PO's expert also confirmed that a hypothetical Factor C recombinant protein produced in HEK293 exhibiting a residual activity below this—for example 14%--would be greater than the reported values for Sf9 and native, but would not satisfy the residual activity requirement of claim 21. EX1067, 61:5-63:10.

A HEK293 recombinantly produced protein that exhibits **both** of those residual activities—for example 9% in the presence of 21 mM sodium citrate and

14% in 16 mM magnesium sulfate would fall within the scope of claim 22 (as it would exhibit a residual activity higher than that of Sf9 and TAL in both ionic solutions (though per claim 22 it need only exhibit a higher residual activity in the presence of one or the other)) *but that same protein would not fall within the scope of claim 21*. This is because that same protein meets neither of the lower bounds of the fixed residual activity range set forth in claim 21. Such additional scope is represented in red and green for each claimed concentration in the annotated version of FIG. 7 above. *See also*, EX1067, 61:5-63:10. Of course, such scope will be variable depending on what values are obtained for residual activity of Sf9-expressed or native. But by vitiating the fixed lower bounds of claim 21 and instead redefining the scope of claim 22 according to the value of variable comparator protein (Sf9 and TAL—both of which were shown based on FIG. 7 to exhibit *very low* residual activities in the presence of ionic solutions), PO impermissibly broadens the scope of an otherwise unsupported and non-enabled claim, and captures claim scope that was not covered by claim 21. PO's Motion should be denied.

B. AMENDED CLAIM 22 WOULD STILL HAVE BEEN OBVIOUS OVER THE PRIOR ART OF THE INSTITUTED GROUNDS.

PO's amended claims would still have been obvious over the prior art at issue in the two instituted Grounds (1 and 2) of this trial.

1. Person of Ordinary Skill in the Art (“POSA”)

PO proposes an alternate definition of a POSA in an apparent attempt to discount Dr. Jain’s background and experience. Dr. Jain has over 18 years of experience in expressing and characterizing recombinant proteins with significant experience in different formats of endotoxin assays. EX1003, ¶2; EX1065, 55:22-56:1, 57:6-8, 58:11-13. He has a vast array of additional experience in this field. EX1065, 59:2-4, 49:20-50:9, 50:12-19, 49:4-6, 63:14-20. Dr. Jain is unquestionably a POSA as of 2013. And all agree that background and experience qualify a POSA rather than specific degree or educational focus. EX1069, 44:19-46:8; EX1067, 27:16-28:11. In any case, PO’s expert conceded that his opinions do not change depending on which POSA definition is used. EX1067, 33:7-11.

2. PO’s Motion Improperly Relies On Expert Testimony From Experts Who Were Unaware of Claim 22

PO’s Motion cites to the Declarations of Dr. Tina Morris and Dr. Brian Schaefer (EXS2042 and 2038) in support the patentability of proposed new claim 22. But neither expert had any awareness of the subject matter of that amended claim when executing their declarations, let alone reviewed it. EX1069, 42:13-43:1; EX1067, 36:1-25. Because neither expert formed any opinions about the subject matter of new claim 22, it was improper for the Motion to rely on their testimony and such reliance should be disregarded.

3. Claim 22 Finds Even Less Support Or Enabling Disclosure From The '767 Application Than Original Claim 21

PO argues that its amended claim 22 is patentable because “substitute claim 22 is entitled to a December 10, 2013 priority date, thus rendering the references relied upon by Petitioner non-prior art.” Motion 7. As discussed in Section I.A., *supra*, however, claim 22 is broader than claim 21 and this enlarged scope does not somehow cure the written description and enablement deficiencies that the Board credited for it to be considering this contingent Motion.

a. If the Claim Requires The Factor C To Have the Claimed Residual Activity In Each of Two Separate Ionic Solutions, There Is No Written Description Support For The Full Scope of Claim 22’s Requirement That *Limulus polyphemus* Factor C Be Higher Than Factor C From Sf9 or Native

The '767 Application contains no disclosure of recombinantly expressing *L. polyphemus* Factor C protein in insect cells, nor what the residual activity of such protein might be. *See generally*, EX1006. The '767 Application also contains no disclosure whatsoever of measuring the residual activity of native *L. polyphemus* Factor C (even though that protein was presumably available). *Id.*

In addition, while the '767 Application provides a single example of residual activity measurements for recombinantly produced *T. tridentatus* Factor C (and Factor C from Sf9 and TAL), and PO insists a POSA could simply extrapolate the data from that species to recombinant *L. polyphemus* Factor C, the '767

Application provides no disclosure or description, *even for T. tridentatus*, of the newly claimed *relationship* between Sf9-produced or native Factor C proteins compared to those recombinantly produced in HEK293 cells. It is also unknown what residual activity values would be generated from *L. polyphemus* Factor C recombinantly produced in Sf9 insect cells or from native *L. polyphemus* proteins. If such values were higher than those values generated for *T. tridentatus*, a POSA could only speculate as to whether the HEK-293 recombinantly produced versions would be higher still. By introducing this unknown and undescribed relationship into new claim 22, PO has improperly added new matter.² As Dr. Jain explained at length, the lack of guidance linking residual activity to some structural feature demonstrates that a POSA would not view the inventors to have possessed the full scope of claim 21, and likewise would not have been in possession of the broader floating comparator aspect of new claim 22. EX1002, ¶¶ 107, 121, 124, 130-135.

b. Proposed Claim 22 is Not Described In the '767 Application

For adequate written description under §120, “[i]t is the disclosures of the applications that count.” *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997) (affirming anticipation based on no written description in priority

² The inventors abandoned their theory regarding *why* mammalian-expressed Factor C exhibited a higher residual activity than insect cells. Pet. 30, 37.

document—“Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed.”); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (district court erred by relying on an undisclosed clinical protocol to support written description ***even though*** it showed that the inventors had invented the claimed invention before the time of filing.”). PO goes ***well beyond*** background knowledge—failing to demonstrate that any of its supplemental evidence was so conventional and well-known as to be excused from its inclusion in the ’767 Application—and improperly augments the ’767 Application with description the inventors unquestionably did not provide.

For example, it is undisputed that the cDNA and amino acid sequence for *Limulus polyphemus* Factor C do not appear in the ’767 Application, nor had they been published by December 10, 2013. EX1006; EX2038, ¶36; EX1067, 32:2-24. PO introduces evidence that bulk sequence data of the whole transcriptome for the *Limulus polyphemus* horseshoe crab (constituting approximately 188.2 million bases, EX2052, 1) had been deposited in the NCBI database by October 31, 2013. POR, 16. This information was not cited in or incorporated into the ’767 Application and PO’s expert did nothing to verify that the sequence information was, in fact, publicly available as of October 31, 2013. EX1067, 95:3-96:14.

Moreover, despite walking through pages of experimental protocols that a POSA “would have” followed to assemble the specific Factor C protein sequence (needle) from the horseshoe crab genome data available at the noted website (haystack), Dr. Schaefer did not actually construct the Factor C sequence that would have been purportedly so easy for a POSA to assemble—claiming it was unnecessary. EX2038, ¶¶61-80; EX1067, 102:24-104:23. Instead, when comparing the sequence information from *Limulus polyphemus* Factor C with that of other horseshoe crab species, Dr. Schaefer used one of³ the sequences provided by the inventors ***in the 2016-filed ’498 PCT to work backward.*** EX1067, 110:17-112:20. That is, the “blaze marks” followed by PO’s witness to understand sequence differences and make predictions about the residual activity of the claimed proteins comes from a document created three years after the ’767 Application. This testimony is plainly fatal to PO’s case, and PO’s supplementation of the ’767 Application with research protocols and experiments a POSA ***could try*** (but no constructed sequence) is inadequate to satisfy the written description requirement for broader claim 22.

³ The ’498 PCT confirms that there were at least 11 known variants of the *Limulus polyphemus* zymogen proteins. EX1005, ¶0195. Dr. Schaefer did not account for these variants in his sequence comparison. EX1067, 99:1-102:23.

PO's supplementation mirrors a similar attempt rejected in *Brita LP v. Int'l Trade Comm'n*, 156 F.4th 1326, 1336 (Fed. Cir. 2025). There, the Federal Circuit affirmed a finding of no written description where the specification did not describe the claimed non-carbon-block filters and rejected patentee's argument that because ***other*** non-carbon-block filter media types were known to those of ordinary skill in the art, less detail was required in the specification. *Id.*

As with the “residual activity” aspect of claim 21, patentee Brita sought to extrapolate a POSAs understanding of the claimed “filter rate and performance” (FRAP) metric from other described carbon-block embodiments to the claimed but undescribed non-carbon-block filter. The Court rejected such gap filling, particularly where different variables contributed to the unpredictability of the FRAP value: “Brita cannot use the knowledge of a skilled artisan to make up for the specification’s lack of disclosure as to non-carbon-block filters that can meet the claimed FRAP factor.” *Id.* Likewise here, PO's attempt to “make up for” the absence of disclosure of recombinantly produced *L. polyphemus* Factor C and ***extrapolate*** that protein's claimed residual activity function based on information about other species of horseshoe crab (where, as discussed below, many variables are implicated) is insufficient under §112.

**c. Even With The Hindsight Benefit of the Known
Limulus polyphemus Factor C Sequence, Differences
In Sequence Were Apparent.**

Using the 2016-reported *Limulus polyphemus* sequence, PO's expert compared that sequence to the sequence for *Tachypleus tridentatus* and *Carcinoscorpius rotundicuada* by running the "Clustal" sequence comparison program and allowing the algorithm of the program to generate outputs with respect to similarities and differences. POR, 18. As expected, there were differences. There were also unknowns. For example, Dr. Schaefer admitted that it was unclear and merely assumed how the algorithm considered charge differences associated with different amino acids. EX1067, 114:12-115:15; 122:22-123:14. And, in characterizing differences in amino acid sequence as "conservative" or "non-conservative" (i.e., those that may have an impact on resulting protein function, and those that likely do not), Dr. Schaefer's interpretation of the Clustal algorithm was not fully consistent with the inventors' own definition of these differences in the '767 Application. EX1067, 116:2-119:17. PO's expert certainly did not look "[to] the four corners of the specification" to discern the extent to which the inventors had possession of the invention as broadly claimed. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). Such is insufficient under § 112, which

requires “an objective inquiry” into the specification itself. *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011).

When asked about *specific differences* in the later-acquired amino acid sequences, including those differences noted by Dr. Jain as giving rise to uncertainty about the resulting function of the Factor C proteins across species (for example, the different amino acids adjacent to the heavy chain cleavage site, EX1002, ¶¶96-97), Dr. Schaefer dismissed such differences or admitted to having not taken such differences into account at all. EX1067, 119:11-120:5 (dismissing a nonconservative mutation in a functional domain where a POSA might “suspect” it would have no functional impact), 138:12-140:5 (dismissing reported amino acid difference in Tokunaga as being “tak[en] with a grain of salt” by a POSA); 141:15-142:9 (admitting that the Phyre 3D-predictive model did not account for the structural difference due to a bulkier tryptophan residue near the Factor C cleavage site in *Tachypleus tridentatus* relative to valine in *Limulus polyphemus*).

PO also identifies no required “structural features” common to the new claim 22. As discussed above, the sequences of different species are undisputedly different and the recombinant production of Factor C generates proteins with inexplicably different residual activities. PO dismisses these differences, but there is no evidence that the inventors understood or described what features (sequence or otherwise) contribute, specifically, to these different residual activity

percentages (*within or between* species). Pet. 27-31. Regardless of how broad the claimed genus is perceived to be, the lack of any actual example (species) within the scope of that claim and the lack of any evidence of a structural feature that drives the full scope of the claimed function across species proves that there is no written description as a matter of law. *See Ariad*, 598 F.3d at 1350.

d. “Functional Interchangeability” Of Native Proteins Is Not Predictive of Residual Activity in Recombinant Proteins

Proposed substitute claim 22 is directed to *recombinantly* produced *L. polyphemus* Factor C with *specific functional capabilities* in specific concentrations of specific ions. But again, the '767 Application contains no description of residual activity in recombinant *Limulus polyphemus* Factor C proteins, and there is no evidence of studies or reports specifically on the “residual activity” metric in horseshoe crab zymogen proteins prior to 2013. EX1006, EX1067, 51:10-24.

Assuming *arguendo* that there was some consensus about the high-level biochemical mechanism of Factor C protein function across species as of December 10, 2013, that knowledge does not facilitate prediction of more specific assay measures such as residual activity. Instead, the evidence demonstrates that even if a POSA was aware of partial similarity in partial amino acid sequencing of *native* Factor C proteins (EX1022, 157), a POSA would not have leaped to the

conclusion that two **recombinantly** produced proteins would have similar properties with respect to residual activity. This is because while various studies prior to 2013 confirmed that native *L. polyphemus* lysate (the LAL test) demonstrated comparable overall detection of endotoxin relative to recombinantly produced Factor C (from, for example, *Carcinoscorpius rotundicuada*), such studies **also revealed** that in the context of specific assays, those proteins behaved differently. EX2035, 21; EX2049, 4; EX2036, 4.

PO cites to US 2003/004432 (EX2035, “the ’432 Publication”) because the authors reported that tryptic peptide sequencing of native *Limulus polyphemus* Factor C protein revealed greater than 90% sequence identity with *Carcinoscorpius rotundicuada*.⁴ However, as the ’432 Publication reports, “[T]he relative factor C activity ratio, the enhancing and inhibiting detergent concentrations [for native *Limulus polyphemus* Factor C] **were different from those in the recombinant Factor C assay.**” EX2035, 21. As reported, the highest enhancement of Factor C activity in Zwittergent (detergent) for rFcCc (~3.75 activity ratio) was at 0.001% concentration (FIG. 1) while the highest enhancement

⁴ Dr. Schaefer acknowledges tryptic peptide sequencing is an incomplete assessment of sequence identification. EX1067, 150:25-151:20.

of Factor C activity ratio in the same detergent for native *Limulus polyphemus* Factor C was ~2.5 activity ratio at a concentration of 0.005% Zwittergent (FIG. 6).

The '432 Publication provides no explanation for this difference, and Dr. Schaefer resisted comparisons, but he acknowledged that a POSA would also not be able to use such information as reported in the '432 Publication to make predictions about residual activity: “detergent and the salt ions in question are completely different entities. So I don’t see where one would take these data and make a specific conclusion about residual activity.” EX1067, 154:12-156:13.

Which is precisely Petitioner’s point because PO cited this reference claiming significance of the reported sequence identity, but the more salient fact is that a POSA would not draw a conclusion about residual activity. *Id.*

Similarly, in Loverock (EX2049), the authors compared endotoxin detection ability between rFcCc (*Carcinoscorpius rotundicuada*) and native *Limulus* lysate (LAL). EX2049, Abstract. While concluding that the two Factor C proteins were “equivalent” when calibrated to the internationally defined standard endotoxin curve, the specific assays performed revealed ***differences*** between the rFcCc and two versions of the LAL assay. EX2049, 4, 5 (“the rFC mean response was significantly different from the two LAL-based procedures.”). Dr. Schaefer concurred that in the specific assay shown in Figure 3 above, the authors “got distinct results” as between LAL and rFcCc. EX1067, 177:10-178:8. Again, he

was “hesitant to draw global solutions [*sic*, conclusions] about LAL versus the recombinant [*Carcinoscorpius rotundicuada* Factor C] based on” such results because, while overall the two proteins may be “functionally comparable,” Dr. Schaefer admits that it “doesn’t mean you can’t come up with an assay and assay conditions here and there where you get a numerical output that is somewhat different.” EX1067, 178:1-21.

This reluctance by Dr. Schaefer to draw conclusions about Factor C function in the context of specific assays exemplifies why a POSA **would not do** what PO insists they would—predict the residual activity in very specific ion concentrations of a brand new recombinantly-produced protein (from *Limulus polyphemus*) based on the reported residual activity of an entirely different species of protein.

Similarly, PO’s cited reference—Alwis—also reported differences in house dust assay results between *Limulus polyphemus* Factor C proteins and recombinantly-produced *Carcinoscorpius rotundicuada* Factor C. EX2036, Abstract, 3.⁵ The authors attributed these reported differences in function to the

⁵ Dr. Shaefer dismissed these differences as potentially attributable to a “universe of possibilities for why they got different results.” EX1067, 164:13-167:4. Dr. Morris provided a similar explanation of the complexity involved in comparing assay results. EX1069, 58:7-59:6.

differences in underlying species of horseshoe crab: “A possible explanation may be differences in the Factor C of the horseshoe crabs that were the source of reagents.” EX2036, 4. Dr. Schaefer dismissed the author’s explanation for such assay difference being attributable to species differences because it appeared in the “discussion” section of the paper. EX1067, 161:18-162:18. But it was **PO** who cited this reference and a POSA would have taken such discussion into account in resisting predictions about assay results across different species of horseshoe crab. Of course, none of the ’432 Publication, Loverock, or Alwis say anything about “residual activity”. EXS2035, 2036, 2049.

Finally, Tokunaga (EX1022), is relied on heavily by PO to argue that a POSA would have understood by 2013 that *Limulus polyphemus* and *Tachypleus tridentatus* native Factor C proteins were “indistinguishable.” POR, 28-29, 37. Tokunaga also does not discuss “residual activity” or recombinant Factor C proteins. Tokunaga does reveal specific and important amino acid **differences** between the partial sequence comparison of native Factor C of these two species, as explained by Dr. Jain in support of the Petition. EX1002, ¶¶95-103. Contrary to Dr. Schaefer’s hindsight speculation (EX2038, ¶30), Tokunaga acknowledges that the sequences of the cleavage sites between chains for *Limulus polyphemus* horseshoe crabs remained, at the time, **unknown**. EX1022, 156-57, FIG. 8S. With respect to the impacts of differences reported in the partial sequence of Tokunaga,

Dr. Morris acknowledged that “there are a lot of factors that impact whether there’s a structural or functional difference or not.” EX1069, 145:17-24; *see also id.* 147:1-9.

Moreover, because the inventors themselves revealed that mammalian-expressed **recombinant** Factor C proteins exhibited residual activities that were significantly different than the native proteins **from the same species** of horseshoe crab with the same sequence (’767 Application, FIG. 7), a POSA would have been extremely reluctant to extrapolate similarities in gross function (i.e., overall ability to detect endotoxin) to more nuanced functional properties under particular conditions (for example, in specific concentrations of particular ions) for recombinantly produced Factor C across **different** species of horseshoe crabs. Dr. Schaefer himself described this unpredictability: “For the...pharmacopeias, when they say ‘functionally interchangeable,’ does that mean that somebody in Japan and somebody in Europe are going to expect an identical result performing the same assay or the same assay with two different species? No, they’re not going to get an identical result.” EX1067, 82:9-19. Taking all this evidence together, a POSA would have agreed with Dr. Jain that any predictions about residual activity in recombinant *Limulus polyphemus* Factor C would have been pure speculation. EX1002, ¶¶84, 91, 102.

PO's heavy supplementation of the '767 Application amounts, at best, to the conclusion that a POSA would deem it obvious to try to produce the claimed recombinant proteins and speculate about their resulting residual activity. The '767 Application does not satisfy § 112 with respect to claim 22. *Lockwood*, 107 F.3d at 1572; *see also In re Kuenzel*, Appeal 2009-015373, 2011 WL 938717, at *5 (B.P.A.I. Mar. 17, 2011); *Ariad*, 598 F.3d at 1352.

e. If The Ionic Concentrations Must Be In the Same Solution, Claim 22 is Not Described

If the amended claim limitation “in the presence of 21 mM sodium citrate and 16 mM magnesium sulfate” is interpreted to mean that the claimed recombinant Factor C have a higher residual activity than the comparator protein in a solution that has ***both*** 21 mM sodium citrate and 16 mM magnesium sulfate that claim lacks written description. That combined solution is nowhere described in the '767 Application, either in any general way or via any working or prophetic example. There is absolutely no contemplation of such an assay or a Factor C protein tested in such a combination solution in the '767 Application and neither of Patent Owner's experts could point to any such support. EX1069, 172:1-173:15; EX1067, 63:11-64:4.

f. The Experimentation Required To Practice Claim 22's Full Scope Is Undue.

As discussed in the Petition (Pet. 35-45), the '767 Application fails to establish how to make and use the full range of claim 21's Factor C proteins (and thus also those with residual activity values falling with the broad range of proteins encompassed by broader claim 22).

Claim 22 covers HEK293 recombinantly-produced *Limulus polyphemus* Factor C proteins with residual activities as low as any value slightly higher than that of *Limulus polyphemus* Factor C recombinantly produced in Sf9 cells or the native *Limulus polyphemus* protein, or as high as any unbounded upper value that still surpasses the Sf9 or native values. PO characterizes this claim as "narrower" (Motion, 12), but as discussed in Section I.A., *supra*, claim 22 is amorphous and undisputedly boasts an exceedingly broad reach. And yet, as with claim 21, none of the '767 Application, PO, nor its experts, has any explanation for a POSA about how to produce such proteins at the lower end of this range, at the middle points of the range, or at the highest points of this range, nor is there any explanation for how to produce such proteins falling with the range as distinct from those falling outside of it. The task of figuring that out is instead left to the POSA to accomplish through significant experimentation. EX1002, ¶¶119-146. Dr. Jain detailed at length why the '767 Application's deficiency in this regard would have required the POSA to have engaged in significant and undue experimentation to

answer these questions as to claim 21, which would also be applicable to broader claim 22. EX1002, ¶¶105-108, 119-126, 131-138, 140-146.

These open-ended claims—with no description of achieving the higher values and no explanation for how to do so by December 10, 2013—are not enabled. *MagSil Corp. v. Hitachi Glob. Storage Inc.*, 687 F.3d 1377, 1383-84 (Fed. Cir. 2012) (no enablement of claims reciting “a change in the resistance by at least 10%” because the specification only enabled changes in resistance up to about 12% yet the claims claimed resistance changes up to infinity); *Epistar Corp. v. Lowes Cos., Inc.*, 2020 WL 771096, at*6-8 (C.D. Cal. Feb. 11, 2020).

4. There is No Evidence of Secondary Considerations That Would Render Claim 22 Non-Obvious As of April 30, 2019.

If claim 22 is found to lack written description support or an enabling disclosure from the '767 Application, that claim (like claim 21) should be entitled to a priority date of no earlier than April 30, 2019 and prior art references Mizumura in combination with either the '498 PCT or McClymont would have rendered claim 22 obvious to a POSA.

PO's only argument for patentability in this scenario is that unexpected results should save claim 22. PO's argument should be rejected for multiple reasons. First, as noted above, PO relies on the testimony of Dr. Morris to support its argument on unexpected results but Dr. Morris had no knowledge of claim 22. Second, PO offers no independent evidence of unexpected results beyond that

offered in support of claim 21 and, as discussed in Petitioner’s IPR Reply (Paper No. 32) (at pages 26-28), that evidence is substantively and legally insufficient to render claim 21 (and broader claim 22) non-obvious. If entitled to a priority date no earlier than April 30, 2019, substitute claim 22 is obvious over the prior art.

C. THE PROPOSED AMENDMENTS RENDER CLAIM 22 INDEFINITE.

Under the standard set forth in *Nautilus, Inc. v. Biosig Instruments, Inc.*, a patent is invalid for indefiniteness if its claims, read in light of the specification and prosecution history, “fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” 572 U.S. 898, 901 (2014).

Alternatively, “[a] claim is indefinite when it contains words or phrases whose meaning is unclear.” *In re Packard*, 751 F.3d 1307, 1310, 1314 (Fed. Cir. 2014). For the reasons discussed below, the claims have unclear meanings and are indefinite under *Packard*. Unlike litigation in district court, IPR proceedings concern patentability, not invalidity. IPRs “are essentially agency reconsideration of a prior patent grant,” *Regents of the Univ. of Minn. v. LSI*, 926 F.3d 1327, 1338 (Fed. Cir. 2019)—in short, “a second look.” *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 279 (2016). There is no basis for applying one definiteness standard upon initial consideration of patentability and a different standard on reconsideration. Post-grant proceedings under the AIA instead implicate “the same

interests as the determination to grant a patent in the first instance.” *Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC*, 584 U.S. 325, 337 (2018).

Proposed claim 22 introduces ambiguity around the required residual activity feature of the claimed Factor C protein and lacks the objective boundaries required by law, under either *Nautilus* or *Packard*.

One interpretation of the phrase “in the presence of 21 mM sodium citrate and 16 mM magnesium sulfate” is that the residual activity of the claimed protein would be that of the protein in a solution of 21 mM sodium citrate and then separately of that same protein in a solution of 16 mM magnesium sulfate.

EX1071, ¶¶3-8, 10. In such case, the claimed Factor C protein would have to meet the residual activity requirement in both types of ionic solution individually. *Id.*

An equally plausible interpretation is that the claimed Factor C protein must have the required residual activity in a single solution that includes both 21 mM sodium citrate and 16 mM magnesium sulfate. *Id.*, ¶¶9, 11.

Because it would not be clear to a POSA which meaning is intended and because the same Factor C protein could satisfy one interpretation but not the other, challenged claim 22 is indefinite and therefore unpatentable. *Id.*, ¶12.

II. CONCLUSION

For the foregoing reasons, entry of proposed claim 22 should be denied.

Respectfully submitted,

Date: 3/2/2026

/Chelsea A. Loughran/

Chelsea A. Loughran, admitted *pro hac vice*
WOLF, GREENFIELD & SACKS, P.C

CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (e)(4)

I certify that on March 2, 2026, a copy of the foregoing document, including any exhibits filed therewith, is being served via electronic mail, as previously consented to by Patent Owner, upon the following:

Alexander B. Stein	alexander.stein@morganlewis.com
Christopher J. Betti	christopher.betti@morganlewis.com
Wan-Shon Lo	shon.lo@morganlewis.com
Maria E. Doukas	maria.doukas@morganlewis.com
Alison Patitucci	alison.patitucci@morganlewis.com
	Seikagaku-CR-IPR-PGR@morganlewis.com

Date: March 2, 2026

/MacAulay Rush/
MacAulay Rush
Paralegal
WOLF, GREENFIELD & SACKS, P.C.