

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

PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND

IPR2025-00440

Patent Owner’s Revised Contingent Motion to Amend

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. SUBSTITUTE CLAIM 22 MEETS THE REQUIREMENTS OF 35 U.S.C. § 316 AND 37 C.F.R. § 42.121	1
A. PO Proposes a Reasonable Number of Substitute Claims	1
B. The Substitute Claim Responds to Patentability Grounds Involved in this Trial	1
C. Substitute Claim 22 Does Not Broaden the Claim Scope or Introduce New Subject Matter	3
1. The Substitute Claim Does Not Broaden the Claim Scope	3
2. The Substitute Claim Does Not Introduce New Matter	4
III. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)	7
IV. CLAIM CONSTRUCTION	8
V. PROPOSED SUBSTITUTE CLAIM 22 IS PATENTABLE	8
A. Substitute Claim 22 Has Ample Written Description Support in the ’767 Application	8
B. The ’767 Application Enables the Full Scope of Substitute Claim 22 of the ’318 Patent	13
1. Substitute claim 22 is Not Broad (<i>Wands</i> Factor 8)	14
2. Quantity of Experimentation Necessary; Amount of Direction or Guidance Presented; Presence or Absence of Working Examples (<i>Wands</i> Factors 1-3)	16
3. Nature of the Invention; State of the Prior Art; and Predictability of the Art (<i>Wands</i> Factors 4, 5, 7)	17
a. Undue Experimentation Would Not Have been Required to Characterize the Sequence of <i>Limulus</i> <i>Polyphemus</i> and Recombinantly Express it in HEK293 Cells Before 2013	17

TABLE OF CONTENTS
(continued)

	Page
4. <i>Wands</i> Factor 6 Supports a Finding that Substitute Claim 22 is Enabled	19
VI. SUBSTITUTE CLAIM 22 IS NOT OBVIOUS UNDER GROUND 1.....	20
VII. SUBSTITUTE CLAIM 22 IS NOT OBVIOUS UNDER GROUND 2.....	22
VIII. CONCLUSION.....	23

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Alcon Rsch. Ltd. v. Barr Lab 'ys, Inc.</i> , 745 F.3d 1180 (Fed. Cir. 2014)	14, 15, 16
<i>BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Organisation</i> , 28 F.4th 1247 (Fed. Cir. 2022)	12, 13
<i>Bos. Sci. Corp. v. Johnson & Johnson</i> , 647 F.3d 1353 (Fed. Cir. 2011)	9
<i>Eli Lilly & Co. v. Teva Pharms. Int'l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	20, 22
<i>Falko-Gunter Falkner v. Inglis</i> , 448 F.3d 1357 (Fed. Cir. 2006)	9, 11
<i>Lectrosonics, Inc. v. Zaxcom, Inc.</i> , IPR2018-01129, Paper 15 (P.T.A.B. Feb. 25, 2019).....	8
<i>Provepharm Inc. v. Wista Lab 'ys Ltd.</i> , No. IPR2018-00323, 2019 WL 2865314 (P.T.A.B. July 2, 2019).....	10
<i>In re Wands</i> , 858 F.2d 731 (Fed. Cir. 1988)	passim
Statutes	
35 U.S.C. § 316.....	1
Other Authorities	
37 C.F.R. § 42.121	1
37 C.F.R. § 42.121(a)(3).....	1

Patent Owner's Revised Contingent Motion to Amend

TABLE OF EXHIBITS

<u>Exhibit No.</u>	<u>Description</u>
2001	Excerpt from U.S. Application No. 14/650,767 File History – Claims dated June 9, 2015
2002	Excerpt from U.S. Application No. 14/650,767 File History – Non-Final Rejection dated September 16, 2016
2003	FAQs for Interim Processes for PTAB Workload Management, available at https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition for European Patent No. 3530670
2005	Notice of Opposition to European Patent No. 3441466
2006	Notice of Opposition to European Patent No. 3530670
2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466
2009	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 17/650,803
2010	Ding, et al., “Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ,” Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/275,777

Patent Owner's Revised Contingent Motion to Amend

2011	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/953,525
2012	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3530670
2013	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in Opposition to European Patent No. 3441466
2014	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 17/650,803
2015	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/275,777
2016	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/953,525
2017	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in Opposition to European Patent No. 3441466
2018	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 17/650,803
2019	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/275,777

Patent Owner's Revised Contingent Motion to Amend

2020	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/953,525
2021	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in Opposition to European Patent No. 3441466
2022	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 17/650,803
2023	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/275,777
2024	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/953,525
2025	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in Opposition to European Patent No. 3441466
2026	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 17/650,803
2027	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/275,777

Patent Owner's Revised Contingent Motion to Amend

2028	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/953,525
2029	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in Opposition to European Patent No. 3441466
2030	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 17/650,803
2031	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/275,777
2032	Tokunaga, 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," (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/953,525
2033	D19 submitted in Opposition to European Patent No. 3441466
2034	U.S. Publication No. 2023/0258647
2035	U.S. Publication No. 2003/0054432

Patent Owner's Revised Contingent Motion to Amend

2036	Alwis, K.U. & Milton, D.K., "Recombinant Factor C Assay for Measuring Endotoxin in House Dust: Comparison with LAL, and (1→3)-β-D-Glucans," Am. J. of Indus. Med. 49:296-300 (2006)
2037	D'Amato A., et al., "In Depth Exploration of the Hemolymph of <i>Limulus polyphemus</i> via Combinatorial Peptide Ligand Libraries," J. Proteome Rsch. (2010), 9:3260-3269
2038	Declaration of Brian C. Schaefer, Ph.D.
2039	Curriculum vitae of Brian C. Schaefer, Ph.D.
2040	Declaration of Wan-Shon Lo
2041	RESERVED
2042	Declaration of Tina Morris, Ph.D.
2043	Curriculum vitae of Tina Morris, Ph.D.
2044	Obst M, et al., Molecular phylogeny of extant horseshoe crabs (Xiphosura, Limulidae) indicates Paleogene diversification of Asian species. Molecular Phylogenetics and Evolution (2012) 62:21-26
2045	TJ Novitsky and H Donald Hochstein, <i>Limulus</i> Endotoxin Test, in Rapid Microbial Methods in the Pharmaceutical Industry, Martin C. Easter, ed. (2005)
2046	Iwanaga S et al., Molecular Mechanism of Hemolymph Clotting System in <i>Limulus</i> , Thromb Res (1992) 68:1-32
2047	T Nakamura and S Iwanaga, Lipopolysaccharide-sensitive serine-protease zymogen (factor C) found in <i>Limulus</i> hemocytes: isolation and characterization, Eur J Biochem (1986) 154:511-521
2048	Tokunaga F et al., Lipopolysaccharide-sensitive serine-protease zymogen (factor C) of horseshoe crab hemocytes, Eur J Biochem (1987) 167:405-416

Patent Owner's Revised Contingent Motion to Amend

2049	Loverock, B et al., A Recombinant Factor C Procedure for the Detection of Gram-negative Bacterial Endotoxin, Pharmacopoeial Forum [Nov.-Dec. 2009] 35(6): 1613-1621.
2050	NCBI BioProject PRJNA178587 https://www.ncbi.nlm.nih.gov/bioproject/PRJNA178587
2051	NCBI BioProject PRJNA178588 https://www.ncbi.nlm.nih.gov/bioproject/PRJNA178588/
2052	NCBI Sequence Read Archive SRX202160 from BioProject PRJNA178588 https://www.ncbi.nlm.nih.gov/sra?LinkName=bioproject_sra_all&from_uid=178588
2053	NCBI Sequence Read Archive for Horseshoe Crab Transcriptome SRR610305 (combined) https://trace.ncbi.nlm.nih.gov/Traces/?view=run_browser&acc=SRR610305&display=metadata https://trace.ncbi.nlm.nih.gov/Traces/?view=run_browser&acc=SRR610305&display=data-access
2054	NCBI SRA entries for SRX202152 and SRX202154 (combined) https://www.ncbi.nlm.nih.gov/sra/?term=srx202152 https://www.ncbi.nlm.nih.gov/sra/?term=srx202154
2055	NCBI BioProjects FAQ https://www.ncbi.nlm.nih.gov/bioproject/docs/faq/
2056	A Brief History of NCBI's Formation and Growth https://www.ncbi.nlm.nih.gov/books/NBK148949/
2057	NLM GenBank and SRA Data Processing https://www.ncbi.nlm.nih.gov/sra/docs/sequence-data-processing/
2058	Marchler-Bauer and SH Bryant, CD-Search: protein domain annotations on the fly, Nucleic Acids Res (2004) 32 (Web Server Issue):W327-31

Patent Owner's Revised Contingent Motion to Amend

2059	Miyata T. et al., Amino Acid Sequence of the Coagulogen from Limulus polyphemus Hemocytes, J. Biol Chem (1984) 259(14):8924-8933.
2060	Cheng, SM et al., Characterization of a complementary deoxyribonucleic acid for the coagulogen of Limulus polyphemus, Biochimica et Biophysica Acta (1986) 868:1-8.
2061	Pharmacopeial Discussion Group https://www.usp.org/harmonized-standards/pdg
2062	Bolden J et al., Currently Available Recombinant Alternatives to Horseshoe Crab blood Lysates: Are they Comparable for the Detection of Environmental Bacterial Endotoxins? A Review. PDA J Pharm Sci and Tech (2020) 74:602-611.
2063	FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, June 2012.
2064	RESERVED
2065	ORCID entry for Shun-ichiro Kawabata https://orcid.org/0000-0002-8772-7522
2066	B. Schaefer, Revolutions in Rapid Amplification of cDNA Ends: New Strategies for Polymerase Chain Reaction Cloning of Full-Length cDNA Ends, Anal Biochem (1995) 227(2):255-273.
2067	Zhu et al., A novel serine protease with clip domain from scallop Chlamys farreri, Mol Biol Rep (2008) 35:257-264.
2068	Kawabata, S., et al., "The lipopolysaccharide-activated innate immune response network of the horseshoe crab," Invertebrate Survival J. (2009), 6(1):59-77

Patent Owner's Revised Contingent Motion to Amend

2069	Novitsky, T.J., “Biomedical Applications of Limulus Amebocyte Lysate,” in , J. Tancredi et al (eds.), <i>Biology and Conservation of Horseshoe Crabs</i> , Springer Science+Business Media, LLC (2010) pp. 315-329
2070	Ding, J.L. and Ho, B., “Endotoxin detection – from <i>Limulus</i> Amebocyte Lysate to Recombinant Factor C,” pp. 187-208 (2010)
2071	RESERVED
2072	International Publication Number WO 2012/118226
2073	Tamura, H., “ <i>EC Bacteriol. Virol. Rsch.</i> 2016,” available at https://ecronicon.net/assets/ecbvr/pdf/ECBVR-01-ECO-03.pdf
2074	Certified English translation of International Publication No. WO 2008/004674 A1
2075	Thorne, et al., “Evaluation of the <i>Limulus</i> Amebocyte Lysate and Recombinant Factor C Assays for Assessment of Airborne Endotoxin,” <i>Appl. Environ. Microbiol.</i> 76(15):4988-95 (2010)
2076	Muta, et al., “Horseshoe Crab Coagulation Factor B, A Unique Serine Protease Zymogen Activated by Cleavage of an Ile-Ile Bond,” (1993) <i>J. Biol Chem.</i> , Vol. 268, No. 28, 21384-88
2077	Muta, et al., “Proclotting Enzyme from Horseshoe Crab Hemocytes, cDNA Cloning, Disulfide Locations, and Subcellular Localization,” (1990) <i>J. Biol Chem.</i> , Vol. 265, No. 36, 22426-33
2078	BE Shakhnovich and EV Koonin, Origins and impact of constraints in evolution of gene families, <i>Genome Res</i> (2006) 16:1529-1536
2079	RESERVED
2080	Rose, T and Di Cera, E, Substrate Recognition Drives the Evolution of Serine Proteases. <i>J Biol Chem</i> (2002). 277(22):19243-19246.

Patent Owner's Revised Contingent Motion to Amend

2081	Clustal alignments of T. tridentatus, L. polyphemus and C. rotundicauda Factor C and T. tridentatus and L. polyphemus Factor B and Pro-clotting enzyme
2082	Sievers F et al., Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega, Molecular Systems Biology 7:539
2083	Dubczak, J., "Standing Guard," Charles River Laboratories, PDA Letter (Sept. 26, 2018)
2084	Iwanaga, S., "Primitive Coagulation Systems and their Message to Modern Biology" (1993) Thromb. Haemost., 70(01):48-55
2085	Nguyen et al., The amino acid sequence of Limulus C-reactive protein. Evidence of polymorphism, J. Biol Chem (1986) 261(22): 10456-10465
2086	Muta et al., Primary structure of anti-lipopolysaccharide factor from American horseshoe crab, Limulus polyphemus, J Biochem (1987) 101(6): 1321-1330
2087	Minetti CA et al., Purification and characterization of an endotoxin-binding protein with protease inhibitory activity from Limulus ameobocytes, J Biol Chem (1991) 266(31): 20773-20780
2088	Liu T et al., Limunectin: A phosphocholine-binding protein from Limulus ameobocytes with adhesion-promoting properties, J Biol Chem (1991) 266:14813-13821
2089	Fujii N et al., Isolation, cDNA cloning, and characterization of an 18-kDa hemagglutinin and ameocyte aggregation factor from Limulus polyphemus, J Biol Chem. (1992) 267(31): 22452-22459
2090	WO92020715A1

Patent Owner's Revised Contingent Motion to Amend

2091	SJ Strong and WR Ellington, Isolation and sequence analysis of the gene for arginine kinase from the chelicerate arthropod, <i>Limulus polyphemus</i> : insights into catalytically important residues, <i>Biochim Biophys Acta</i> (1995) 1246(2): 197-200
2092	Munger SD et al., Molecular and immunological characterization of a Gq protein from ventral and lateral eye of the horseshoe crab <i>Limulus polyphemus</i> , <i>Invert Neurosci.</i> (1996) 2(3):1 75-182
2093	Chen FH et al., Molecular cloning of a putative cyclic nucleotide-gated ion channel cDNA from <i>Limulus polyphemus</i> , <i>J Neurochem.</i> (1999) 72(2): 461-471 (1999)
2094	Reid EA et al., Molecular cloning and identification of a putative PKC epsilon cDNA from <i>Limulus polyphemus</i> brain, <i>Life Sci</i> (2003) 72(8): 961-976
2095	Blackburn DC et al., Isolation and Expression of Pax6 and atonal Homologues in the American Horseshoe Crab, <i>Limulus polyphemus</i> , <i>Dev Dyn</i> (2008) 237(8): 2209-19
2096	NCBI Nucleotide search results for <i>limulus polyphemus</i> released prior to December 10, 2013
2097	RESERVED
2098	BLAST hits and CD-Search results for Factor C against SRR610305 (figure/diagrams)
2099	Opposition submitted in EP3530670 dated November 21, 2025
2100	Predicted 3-D structure comparisons for <i>Limulus polyphemus</i> and <i>Tachypleus tridentatus</i> Factor C
2101	U.S. Patent No. 10,473,663
2102	A Yoneda and T Kurokawa, A sensitive sandwich ELISA to measure (1→3)-β-D-glucan levels in blood, <i>J Immun Meth</i> (2011) 365:158-165

Patent Owner's Revised Contingent Motion to Amend

2103	Graphical depiction of Clustal alignment of <i>Limulus polyphemus</i> , <i>Carcinoscorpius rotundicauda</i> , and <i>Tachypleus tridentatus</i> Factor C sequences
2104	U.S. Pharmacopoeia Ch. <85> “Bacterial Endotoxins Test” (Dec. 1, 2012)
2105	European Pharmacopoeia 5.0, “2.6.14. Bacterial Endotoxins,” 01/2005:20614
2106	Excerpts from Japanese Pharmacopoeia-XV, “4.01 Bacterial Endotoxins Test” (March 31, 2006)
2107	Findlay, L., et al. “Collaborative study for the establishment of the WHO 3 rd International Standard for Endotoxin, the Ph. Eur. Endotoxin biological reference preparation batch 5 and the USP Reference Standard for Endotoxin Lot H0K354”
2108 [NEW]	Second Declaration of Brian Schaefer, Ph.D.

I. INTRODUCTION

In view of Petitioner's ("CRL") Opposition (Paper 33, "Opp.") to Patent Owner's ("PO") Contingent Motion to Amend (Paper 27) and the Board's Preliminary Guidance ("Preliminary Guidance") (Paper 34), PO respectfully submits this revised contingent motion to amend. Should the Board hold claim 21 unpatentable, PO submits that this Motion demonstrates the patentability of substitute claim 22 presented herein (Appendix A). Specifically, narrowed substitute claim 22 finds Section 112 support to be afforded a December 10, 2013 priority date, thus eliminating the references relied upon by Petitioner in its unpatentability grounds as prior art.

II. SUBSTITUTE CLAIM 22 MEETS THE REQUIREMENTS OF 35 U.S.C. § 316 AND 37 C.F.R. § 42.121

A. PO Proposes a Reasonable Number of Substitute Claims

As shown in Appendix A, PO proposes one substitute claim for the single challenged claim. This Motion thus abides by the general presumption that "only one substitute claim [would] be needed to replace each challenged claim." 37 C.F.R. § 42.121(a)(3).

B. The Substitute Claim Responds to Patentability Grounds Involved in this Trial

Substitute claim 22 responds to Petitioner's arguments that claim 21 of the '318 Patent is not entitled to its December 10, 2013 priority date because the '767

IPR2025-00440

Patent Owner's Revised Contingent Motion to Amend

Application does not provide adequate written description support or enable the full scope of the claim. Petitioner's Section 112 arguments include its assertion that the inventors did not possess the full scope of the claimed residual activity range or enable this full range without undue experimentation. *See, e.g.*, Pet. at 5.

This amendment directly responds to that argument by narrowing the residual activity limitations to overcome the priority date challenge, thus rendering Petitioner's unpatentability grounds moot because the relied-upon references are not prior art.¹ Moreover, as discussed *infra*, should the Board credit Petitioner's Section 112 arguments that "any predictions about residual activity in recombinant *Limulus polyphemus* Factor C would have been pure speculation," Opp. at 26, such that substitute claim 22 is not entitled to the 2013 priority date, Petitioner's unpatentability grounds 1 and 2 fail on their merits because (i) they do not disclose the revised residual activity limitations and (ii) the reasonable expectation of success analysis would run afoul of Petitioner's Section 112 analysis.

¹ As discussed *infra*, the priority date arguments regarding the claimed species of horseshoe crab (*L. polyphemus*) likewise fail.

C. Substitute Claim 22 Does Not Broaden the Claim Scope or Introduce New Subject Matter

1. The Substitute Claim Does Not Broaden the Claim Scope

Substitute claim 22 does not broaden the claim scope because it adds a further narrowing limitation while maintaining the lower limits of the recited residual activity. Like original claim 21, substitute claim 22 requires the *Limulus polyphemus* Factor C protein expressed from HEK293 to exhibit a residual activity of “at least one selected from a group consisting of” two different options. The options in original claim 21 are (i) 10% or higher in the presence of 21 mM sodium citrate or (ii) 15% or higher in the presence of 16 mM magnesium sulfate. Ex. 1001 at cl. 21.

Claim 22 narrows the scope of claim 21 by ***requiring the further limitation*** that in each respective salt solution, the residual activity of the Factor C expressed in the HEK293 cell must be ***higher*** than either *Limulus polyphemus* Factor C expressed in Sf9 as a host cell or ***higher*** than native *Limulus polyphemus* Factor C. It also maintains the fixed lower limits of recited residual activities in the salt solutions claimed in claim 21 by excluding any Factor C protein exhibiting a residual activity below 10% in the presence of 21 mM sodium citrate or below 15% in the presence of 16 mM magnesium sulfate.

Proposed substitute claim 22 thus addresses the Board's concerns noted in its Preliminary Guidance, Paper 34 at 6-7, and renders moot Petitioner's arguments in its Opposition. Opp. at 1-2. It ***excludes any*** HEK293-expressed *Limulus*

Patent Owner's Revised Contingent Motion to Amend

polyphemus Factor C proteins with residual activity values falling outside the scope of original claim 21 while incorporating the further narrowing limitation relating to comparator proteins.

2. The Substitute Claim Does Not Introduce New Matter

Substitute claim 22 does not introduce new subject matter but is instead supported by, not only the '318 Patent specification but also the priority '767 Application.² The specification includes a section titled “*Modes for Carrying Out the Invention*” that states the “Factor C of the present invention is a *Factor C derived from a horseshoe crab*” and specifically identifies *Limulus polyphemus* as a known species. Ex. 1001 at 13:5-6, 13:22-34. It further includes a specific example titled “Expression of Factor C in mammalian cells (HEK293),” describing steps to produce Factor C using HEK293 cells as the host cell—the same host cell substitute claim 22 recites. *Id.* at 31:14-43.

The specification further explains the “present inventors have found that a recombinant horseshoe crab Factor C can be produced by use of human cells . . . and that endotoxin can be measured by use of the thus-produced recombinant Factor C

² Petitioner concedes the '318 Patent specification and the '767 Application specification are identical. Pet. at 21-22. Citations to the '318 Patent thus necessarily include statements also present in the '767 Application.

Patent Owner's Revised Contingent Motion to Amend

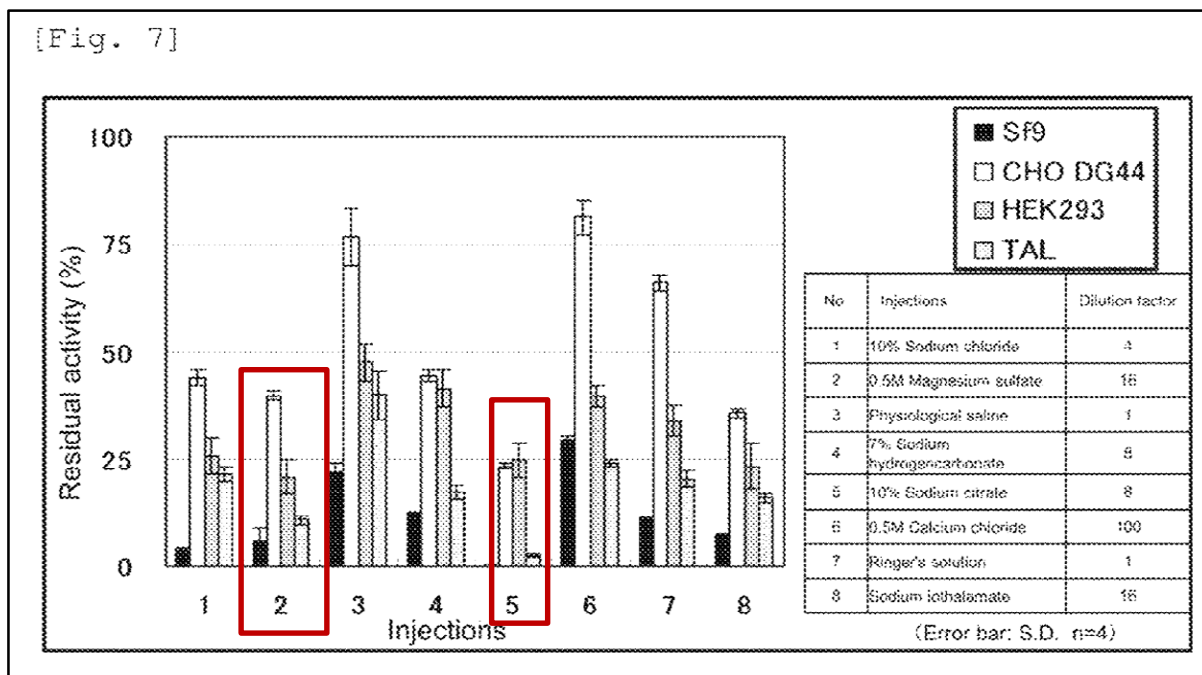
while reaction inhibition in the presence of a salt (ion) is mitigated.” Ex. 1001 at 3:13-18. The specification continues, stating the “present invention encompasses the following modes” and then lists a number of modes, including recombinantly produced in HEK293 cells (i) Factor C exhibiting a residual activity of 10% or higher in the presence of 21 mM sodium citrate; (ii) Factor C exhibiting a residual activity of 15% or higher in the presence of 16 mM magnesium sulfate; (iii) Factor C exhibiting a **higher** residual activity in the presence of 21 mM sodium citrate as compared to Factor C expressed in Sf9 cells and/or a native Factor C; and (iv) Factor C exhibiting a **higher** residual activity in the presence of 16 mM magnesium sulfate as compared to Factor C expressed in Sf9 cells and/or a native Factor C. *Id.* at 3:19-12:11.

The specification further explains that the “Factor C of the present invention may have low susceptibility to inhibition of activity by an ion” and that this “refers to the state that the Factor C of the present invention exhibits a high residual activity in the presence of an ion.” Ex. 1001 at 17:20-24. The specification expressly identifies recombinant Factor C expressed in insect cell Sf9 and native Factor C, which are the two comparators added to substitute claim 22, as examples of this control Factor C. *Id.* at 4:5-9, 4:21-25.

The specification further includes an example titled “Inhibition of activity by injection” that details measuring the residual activity of Factor C in salt solutions,

Patent Owner's Revised Contingent Motion to Amend

including the claimed 21 mM sodium citrate and 16 mM magnesium sulfate. Ex. 1001 at 34:39-35:43. The specification details the procedure used for this measurement in Figure 4 and provides results in Figure 7 that show that expression of Factor C in HEK293 cells resulted in higher residual activity in each of the claimed salt solutions as compared to corresponding (i) Factor C expressed in Sf9 cells and (ii) native Factor C. *Id.* at Fig. 7. The results also show the Factor C in HEK293 cells that had higher residual activity than Factor C in Sf9 cells and native Factor C did not have a residual activity less than 10% in the presence of 21 mM sodium citrate or a residual activity less than 15% in the presence of 16 mM magnesium sulfate. *Id.* at Fig. 7.



Ex. 1001 at Fig. 7 (annotated).

The specification also explains that “[r]ecombinant Factor C (CHO) and recombinant Factor C (HEK) showed a tendency to have low susceptibility to reaction inhibition to all the tested injections, *as compared with native Factor C (TAL). . . . In contrast, recombinant Factor C (Sf9) was most susceptible* to reaction inhibition in many injections (7 injections except sample No. 6).” Ex. 1001 at 35:31-38.

While the data in Figure 7 relates to Factor C from *Tachypleus tridentatus*, not the claimed *Limulus polyphemus*, as discussed more below, incorporated here, a POSA would have understood Factor C proteins are highly conserved among horseshoe crab species such that Factor C from *Limulus polyphemus* would also exhibit the claimed residual activity limitations. As such, proposed substitute claim 22 does not introduce new matter.

III. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

In this motion, as in the PO Response, PO proposes the following definition of a POSA: a POSA would have a Ph.D. in molecular biology, biochemistry, or enzymology and at least two years of experience with cloning genes, expressing cloned genes as proteins, and characterizing them. Ex. 2038 ¶ 49. The POSA may also collaborate with others, including those with specific experience in conducting structure-function analyses of enzyme function, evaluating the activity of horseshoe

Patent Owner's Revised Contingent Motion to Amend

crab zymogen proteins individually, or in a cascade reaction for endotoxin detection and quantitation. *Id.*

IV. CLAIM CONSTRUCTION

In this Motion, Patent Owner agrees that the terms in substitute claim 22 can be afforded their plain and ordinary meaning.

V. PROPOSED SUBSTITUTE CLAIM 22 IS PATENTABLE

Petitioner bears the burden of showing that the substitute claims are unpatentable. *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 4 (P.T.A.B. Feb. 25, 2019) (precedential). Nonetheless, PO asserts that the contingent substitute claim 22 is patentable over the cited prior art because substitute claim 22 is entitled to a December 10, 2013 priority date, thus rendering the references relied upon by Petitioner non-prior art.

A. Substitute Claim 22 Has Ample Written Description Support in the '767 Application

As discussed in Section II.C.2, *supra*, incorporated here, the specification provides ample description of the scope of claim 22 such that a POSA would have understood the inventors had possession of the invention at least by the 2013 filing date of the '767 Application. Ex. 2038 ¶¶ 52-60; Ex. 2108 ¶¶ 8-13. Petitioner's argument that 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,"

Opp. at 8-9, ignores the ample support in the specification described above, such as Figure 7.

Petitioner's reliance on the '767 Application's lack of working examples specific to *Limulus polyphemus* Factor C, Opp. at 8-11, also falls flat, as "the absence of examples . . . **does not** render the written description inadequate" and "actual reduction to practice is **not required** for written description." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Moreover, "a patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement," because "the specification is viewed from the perspective of one of skill" in the relevant art. *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011).

Factor C protein from *Limulus polyphemus* had been successfully isolated and characterized, as well as compared to Factor C from the *Tachypleus tridentatus* horseshoe crab as early as the 1990s. *See, e.g.*, Ex. 1022 at 150; Ex. 1025. Moreover, by October 31, 2012, researchers at the University of Connecticut had sequenced and deposited (i) a 188 Mb *Limulus polyphemus* cDNA amoebocyte transcriptome under BioProject accession number PRJNA178588; and (ii) a 4 Gb shotgun sequence of the *Limulus polyphemus* genome under BioProject accession number PRJNA178587. Ex. 2038 ¶¶ 36, 61. This sequence information was publicly

IPR2025-00440
Patent Owner's Revised Contingent Motion to Amend

available by at least **October 31, 2013**. *Id.* ¶ 37; Ex. 2052; Ex. 2053; Ex. 2054; Ex. 2057.

Petitioner does not contest the existence of this sequence information, nor can it. Instead, Petitioner argues that “PO goes *well beyond* background knowledge” and “improperly augments the ’767 Application.” Opp. at 10 (emphasis in original). Not only does Petitioner fail to support these conclusions, but its argument contradicts arguments it made before the EPO in Opposition proceedings regarding the routine nature of characterizing the *Limulus polyphemus* Factor C sequence.³ Ex. 1048 ¶¶ 4, 30-37, 51, 56, 59. Any attempt here by Petitioner to assert the opposite should thus be viewed with skepticism and undermining Petitioner’s credibility. *See Provepharm Inc. v. Wista Lab’ys Ltd.*, No. IPR2018-00323, 2019 WL 2865314, at *15 (P.T.A.B. July 2, 2019).

As PO’s expert Dr. Schaefer explains, a POSA would have been capable of assembling **97.2% of the full Factor C coding sequence** based on the known similarities between *Tachypleus tridentatus* and *Limulus polyphemus*, as well as based on the publicly available University of Connecticut sequence information. Ex.

³ After PO filed two motions to compel additional discovery (Paper Nos. 12, 23), Petitioner finally confirmed that it “is ‘the party behind the European Opposition proceeding.’” Paper 31 at 2.

IPR2025-00440

Patent Owner's Revised Contingent Motion to Amend

2038 ¶¶ 61-64. As Dr. Schaefer further explains, as of December 10, 2013, a POSA could have easily recovered the remaining sequence by applying standard methods well within the skill of a POSA. *Id.* ¶¶ 65-81. That the '767 Application did not expressly recite this sequence information is irrelevant to the written description analysis. *See, e.g., Falko-Gunter*, 448 F.3d at 1367-68.

As Patent Owner's expert Dr. Schaefer further explains, a POSA would have expected as of December 10, 2013 that key regions encoding functional units of Factor C and motifs for its interaction with partner proteins would be ***highly conserved*** across species of horseshoe crabs. Ex. 2038 ¶ 85; *see also id.* ¶ 20 (noting horseshoe crabs evolved slowly earning a "living fossils" moniker); *id.* ¶¶ 86-91. Indeed, as Dr. Schaefer notes, out of 1,020 amino acids, there are only ***11 non-conservative substitutions*** in either *C. rotundicauda* or *T. tridentatus* Factor C, with only ***5 within identified conserved domains***. *Id.* ¶¶ 90-97; Ex. 2081.

Thus, a POSA would have understood that the functional domains are highly conserved between species of horseshoe crab such that the species exhibited a high degree of functional similarity. Ex. 2038 ¶¶ 85-102; Ex. 2108 ¶ 13. A POSA would have also understood that, despite the geographical and general physical or genetic differences across the species of horseshoe crabs, the coagulation cascade proteins (*e.g.*, Factor C) were structurally similar and functionally identical across species. Ex. 2038 ¶¶ 86-88, 98-102. Indeed, the US, European, and Japanese Pharmacopeia

Patent Owner's Revised Contingent Motion to Amend

reflect the understanding in the art that the coagulation cascade and its constituent proteins are functionally identical between *Limulus polyphemus* and *Tachypleus tridentatus*. Ex. 2104 at 1; Ex. 2105 at 1; Ex. 2106 at 4; Ex. 2038 ¶ 100.

A POSA would have therefore understood that even though Figure 7 in the '767 Application depicts residual activity of *Tachypleus tridentatus* Factor C, because of the highly conserved nature of species, the claimed residual activity in claim 22 would also be expected in *Limulus polyphemus* Factor C. Ex. 2108 ¶ 13.

BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Organisation, is instructive. 28 F.4th 1247, 1265 (Fed. Cir. 2022). In *BASF*, the Federal Circuit affirmed written description support existed for claims directed to producing LC-PUFAs in a specifically claimed species of plant cells—canola—despite the specification lacking a working example of production in that species. *Id.* at 1264-1268. Much like the facts here where the '767 Application identifies *Limulus polyphemus* Factor C as an embodiment of the invention, Paper 26 at 26-27, the specification in *BASF* identified canola as an embodiment of the invention. 28 F.4th at 1264-1268. While the specification in *BASF* did not include an example of using canola to produce LC-PUFAs, as the Court explained, “actual reduction to practice is not a requirement of possession.” *Id.* at 1267-1268. Moreover, the Court noted the specification's working examples of another species (*Arabidopsis*) supported a holding of adequate written description for the different canola species because

Patent Owner's Revised Contingent Motion to Amend

substantial evidence existed that *Arabidopsis* is a reliable model for canola and highly predictive of positive results in canola. *Id.* at 1265-1266. Here, while the '767 Application examples focus on *Tachypleus tridentatus*, as PO and its expert explain, given the high similarity between the species, a POSA would have expected residual activity to be maintained across species.

Thus, the knowledge of a POSA at the time of the '767 Application and the disclosures in the application itself, provide adequate written description support for substitute claim 22.⁴

B. The '767 Application Enables the Full Scope of Substitute Claim 22 of the '318 Patent

To assess whether undue experimentation is required, courts examine a number of factual considerations referred to as the *Wands* factors, which include (i) the quantity of experimentation necessary, (ii) the amount of direction or guidance presented, (iii) presence or absence of working examples, (iv) nature of the invention, (v) state of the prior art, (vi) relative skill of those in the art, (vii)

⁴ PO's claim 22 in Appendix A removes any interpretation that residual activity must be present in a single solution containing *both* 21 mM sodium citrate and 16 mM magnesium sulfate, thus addressing the Board's concern noted in the Preliminary Guidance, Paper 32 at 12, and obviating Petitioner's indefiniteness argument, Opp. at 24-25.

Patent Owner's Revised Contingent Motion to Amend

predictability or unpredictability of the art, and (viii) breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A proper analysis of the *Wands* factors demonstrates that undue experimentation would **not** have been required, and the '767 Application enables the full scope of substitute claim 22.

1. Substitute claim 22 is Not Broad (*Wands* Factor 8)

Substitute claim 22 is **narrowly** confined to a specific species of horseshoe crab (*Limulus polyphemus*) recombinantly expressed from a specific host cell (HEK293) with a higher residual activity in specifically claimed concentrations of specific salt solutions as compared to specifically identified control Factor C whereby the claim excludes Factor C proteins falling below fixed lower limit of residual activities specific to the salt solution. It does **not** encompass a broad genus.

To the extent Petitioner argues that the residual activity requirement in substitute claim 22 provides a broad range that is not enabled, its argument fails. Claim 22 simply requires a comparative analysis such that the inventive Factor C's residual activity in HEK293 cells is **higher** than residual activity in control Factor C (*i.e.*, Factor C in Sf9 cells or native Factor C) while maintaining the lower residual activity limit.

As the Board noted in its Preliminary Guidance, the comparator language appears close to the claim in *Alcon Rsch. Ltd. v. Barr Lab 'ys, Inc.*, where the Federal Circuit found the claim enabled. 745 F.3d 1180 (Fed. Cir. 2014). Paper 34 at 13-

14. In *Alcon*, the claims required “some increase in chemical stability.” *Alcon*, 745 F.3d at 1189. In reversing the district court’s finding of non-enablement, the Federal Circuit noted the district court’s reliance on “variables” that *may* affect the chemical stability. *Id.* As the Court explained, while those variables “may be relevant to *optimizing* the stability” of the composition, there was no evidence adduced that those variables would be necessary “in order to *practice* the claimed invention” that merely required some increase in chemical stability, not a particular magnitude of increase. *Id.*

The same analysis applies here. Substitute claim 22 requires the inventive Factor C expressed in HEK293 cells be ***higher*** than control Factor C. The specification provides ample support teaching a POSA how to make and use the invention to *practice* the invention as claimed. *See* Section II.C.2.

Further, the language in claim 22 excluding proteins that have residual activity less than 10% in 21 mM sodium citrate or less than 15% in 16 mM magnesium sulfate does not change the analysis or require enablement of a wide range of residual activities. While this language sets a floor for the residual activity, the key aspect of claim 22 is providing a residual activity for the inventive HEK293-expressed Factor C that is ***higher*** than control Factor C without requiring a particular magnitude of increased residual activity.

Any argument by Petitioner that enablement requires producing proteins across a broad range must therefore be rejected.

2. Quantity of Experimentation Necessary; Amount of Direction or Guidance Presented; Presence or Absence of Working Examples (*Wands* Factors 1-3)

The law does not require working examples to find enablement, *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189-1190 (Fed. Cir. 2014), and the '767 Application provides examples that a skilled artisan would have used as a roadmap to practice the full scope of the claimed invention without undue experimentation. The '767 Application describes producing Factor C in mammalian cells, including HEK293 cells, and discusses a specific example detailing the production of recombinant Factor C in HEK293 cells. Ex. 1006 at 53-54, 87-88. It also provides a specific procedure in Figure 4 for measuring Factor C activity and discloses a specific example where the residual activity of recombinantly produced Factor C, including Factor C expressed in HEK293 cells, was measured in the claimed salt solution concentrations and determined to be higher than the residual activity of the control Factor C while not falling outside the scope of the lower limits set by claim 22. Ex. 1006 at 96-99, Figs. 4, 7.

With the specification's guidance, a skilled artisan would have known how to use HEK293 cells to recombinantly express Factor C and how to measure the residual activity of the Factor C in the claimed salt solution concentrations to achieve

Patent Owner's Revised Contingent Motion to Amend

the residual activity limitations of claim 22. Ex. 2038 ¶¶ 114-118; Ex. 2108 ¶¶ 14-16. The lack of examples using *Limulus polyphemus* Factor C does not change the conclusion. Given what was well known in the prior art and the admitted high level of skill, a skilled artisan could have implemented the specification's teachings to make and use the claimed Factor C from *Limulus polyphemus* without undue experimentation. Ex. 2038 ¶ 116.

In sum, the specification would have enabled a skilled artisan to make and use Claim 22 because (i) undue experimentation had not been required to practice the invention, and (ii) the specification provides direction and examples regarding expression of Factor C in HEK293 cells and measuring residual activity in the claimed salt solutions.

**3. Nature of the Invention; State of the Prior Art; and
Predictability of the Art (*Wands* Factors 4, 5, 7)**

Wands factors 4, 5, and 7 further support that substitute claim 22 is enabled. Ex. 2038 ¶¶ 111-112; Ex. 2108 ¶ 16.

**a. Undue Experimentation Would Not Have been
Required to Characterize the Sequence of *Limulus
Polyphemus* and Recombinantly Express it in
HEK293 Cells Before 2013**

As discussed, the '767 Application describes examples of recombinantly expressing Factor C in HEK293 cells. *See, e.g.*, Ex. 1006 at 53-54, 87-88. Additionally, as discussed, more than *two decades* before the 2013 filing date of the

'767 Application, Dr. Tokunaga and his group had already isolated Factor C from *Limulus polyphemus* and compared its properties and amino acid compositions with those of *Tachypleus tridentatus*—the same species of horseshoe crab used in the examples in the '767 Application. Ex. 1022 at 150-151, 155. As Dr. Tokunaga reported, the “immunological and biochemical properties” of the purified Factor C from *Limulus polyphemus* are “*indistinguishable*” from those of Factor C isolated from *Tachypleus tridentatus*, and “the individual amino acid compositions of the two proteins and of their chain subunits were *indistinguishable*.” Ex. 1022 at 150-151, 153.

Moreover, in 2003, researchers had successfully isolated Factor C from *Limulus polyphemus* and determined that “the *Limulus* factor C sequence closely matched the *Asian species, with >90% sequence identity*.” Ex. 2035 at [0134]. Additionally, by December 10, 2013, the information available from public sources would have allowed a POSA to arrive at the cDNA sequence of *Limulus polyphemus* Factor C through routine experimentation. Ex. 2038 ¶¶ 58-60.

Given the state of the prior art and the nature of the invention, a POSA would have had a ready, working knowledge of the sequence and the immunological and biochemical properties of *Limulus polyphemus* to practice the full scope of substitute claim 22 without undue experimentation. Ex. 2038 ¶¶ 111-112; Ex. 2108 ¶¶ 14-16.

Patent Owner's Revised Contingent Motion to Amend**4. *Wands* Factor 6 Supports a Finding that Substitute Claim 22 is Enabled**

As even Petitioner's expert admits, recombinant technology was well known in 2013. *See, e.g.*, Ex. 1002 ¶ 5 (describing his work in 2006-2008 "evaluat[ing] the recombinant Factor C endotoxin kit"). Moreover, as discussed, the '767 Application describes the process for making recombinant Factor C using HEK293 cells and provides a procedure for assessing whether the recombinantly produced Factor C in HEK293 cells demonstrates higher residual activity than control Factor C in the claimed salt solution concentrations. Given the admitted high skill of a POSA, she would not have had to unduly experiment to design, express, and test recombinant Factor C proteins, particularly in view of the roadmap provided by the '767 Application.

As such, under the *Wands* factors, the '767 Application teaches how to make and use the full scope of substitute claim 22 without undue experimentation and thus enables the claim.

Accordingly, the '767 Application provides written description support and enables the full scope of substitute claim 22 of the '318 Patent such that it should be afforded its December 10, 2013 priority date. With this proper priority date applied, none of the art relied upon by Petitioner in its two invalidity grounds qualifies as prior art and both grounds fail.

VI. SUBSTITUTE CLAIM 22 IS NOT OBVIOUS UNDER GROUND 1

To the extent the Board determines that substitute claim 22 is not entitled to the December 10, 2013 priority date such that Mizumura and the '498 PCT are prior art, Petitioner's invalidity challenge still fails because Petitioner failed to meet its burden to demonstrate claim 21 is unpatentable.

As Petitioner concedes, Mizumura's disclosure "is identical to both the '767 Application and the '318 patent specification." Pet. at 45. Claim 22 recites residual activity limitations for *Limulus polyphemus* Factor C, but the data presented in Figure 7 relates to *Tachypleus tridentatus* Factor C. While Petitioner may assert, as it does for claim 21, that a POSA would have been motivated to modify Mizumura with the teaching of the '498 PCT to develop recombinant *Limulus polyphemus* Factor C via HEK293 cells with the residual activity described in Mizumura and would have had a reasonable expectation of success in using *Limulus* constructs to generate the claimed residual activity, this argument contradicts Petitioner's arguments rebutting Section 112 support.

Petitioner bears the burden of demonstrating unpatentability and that a POSA would have had a reasonable expectation of success in arriving at the claimed invention. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1348 (Fed. Cir. 2021). But Petitioner's reasonable expectation of success theory cannot be squared with its assertions relating to the lack of Section 112 support for the claims.

IPR2025-00440

Patent Owner's Revised Contingent Motion to Amend

Indeed, Petitioner cannot argue as it does in its Opposition to the Motion to Amend that PO cannot “‘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” to support a Section 112 attack, Opp. at 12, but then turn around and argue the same type of extrapolation can be performed to support a reasonable expectation of success in achieving the claimed residual activity with *Limulus polyphemus* Factor C based on the prior art’s disclosure of residual activity values for *Tachypleus tridentatus*.

Moreover, Petitioner devotes over five pages of its Opposition to arguing that “a POSA would not have leaped to the conclusion that two ***recombinantly*** produced proteins would have similar properties with respect to residual activity.” Paper 32 at 15-20. Indeed, Petitioner expressly states “a POSA ***would not do*** what PO insists they would—predict the residual activity in very specific ion concentrations of a new-recombinantly produced protein (from *Limulus polyphemus*) based on the reported residual activity of an entirely different species of protein.” *Id.* at 18. Petitioner further states “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.***” *Id.* at 18-19.

IPR2025-00440

Patent Owner's Revised Contingent Motion to Amend

These arguments directly undermine Petitioner's obviousness case. The prior art says *nothing* about the residual activity of recombinantly-produced *Limulus polyphemus* Factor C in the very specifically claimed ion concentrations, so Petitioner is forced to rely on residual activity data for recombinantly-produced *Tachypleus tridentatus* Factor C described in Mizumura. Petitioner cannot, as it does, argue a POSA would not predict residual activity for recombinantly produced Factor C of one species based on data from another recombinantly produced Factor C from another species but then also argue a reasonable expectation of success exists to arrive at the claimed invention. These arguments simply cannot be reconciled.

Because of these inconsistent positions, Petitioner's reasonable expectation of success arguments should be rejected. Petitioner has thus failed to demonstrate a reasonable expectation of success to support its obviousness argument. *See Eli Lilly*, 8 F.4th at 1348.

VII. SUBSTITUTE CLAIM 22 IS NOT OBVIOUS UNDER GROUND 2

For the same reasons as discussed in Ground 1, incorporated here, Petitioner failed to meet its burden to demonstrate a reasonable expectation of success in modifying Mizumura in view of McClymont to arrive at the claimed invention because its arguments in Opposition for lack of Section 112 support contradict its obviousness arguments.

VIII. CONCLUSION

For reasons discussed above, if the Board should find claim 21 of the '318 Patent unpatentable, the Board should issue substitute claim 22 and maintain its patentability.

Respectfully Submitted,

Dated: April 13, 2026

/ Alexander B. Stein /
Alexander B. Stein, Reg. No. 71,397

IPR2025-00440

Patent Owner's Revised Contingent Motion to Amend

CERTIFICATE OF PAGE LIMIT

I, the undersigned, certify that the foregoing Patent Owner's Revised Contingent Motion to Amend complies with the page limits of 37 C.F.R. § 42.24(a) because it does not contain more than 25 pages. This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and the type style requirements of 37 C.F.R. § 42.6(a)(2)(iii) and (iv).

Respectfully Submitted,

Dated: April 13, 2026

/ Alexander B. Stein /
Alexander B. Stein, Reg. No. 71,397

Patent Owner's Revised Contingent Motion to Amend

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on April 13, 2026, a copy of this PATENT OWNER'S REVISED CONTINGENT MOTION TO AMEND was served via the email correspondence address of record for Petitioner's counsel of record:

Scott A. McKeown (SMcKeown-PTAB@wolfgreenfield.com)

Flora Luo (FLuo-PTAB@wolfgreenfield.com)

Chelsea A. Loughran (CLoughran-PTAB@wolfgreenfield.com)

Respectfully Submitted,

Dated: April 13, 2026

/ Alexander B. Stein /

Alexander B. Stein, Reg. No. 71,397

APPENDIX A – SUBSTITUTE CLAIM

The proposed substitute for claim 21 is shown in marked-up form below. Underlining indicates proposed additions to the original claim 21 and double brackets indicate proposed deletions from the original claim 21.

Claim 22. [Proposed substitute for claim 21] A horseshoe crab Factor C protein having activity of Factor C,

wherein the horseshoe crab is *Limulus polyphemus*, and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell, and

wherein the Factor C protein exhibits 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]] a residual activity in the presence of 21 mM sodium citrate that is:

(i) higher than the residual activity in the presence of 21 mM sodium citrate of a corresponding *Limulus polyphemus* Factor C protein expressed in Sf9 as a host cell, or

(ii) higher than the residual activity in the presence of 21 mM sodium citrate of a native *Limulus polyphemus* Factor C protein.

Patent Owner's Revised Contingent Motion to Amend

wherein the horseshoe crab Factor C protein is not a horseshoe crab Factor C protein having less than 10% residual activity in the presence of 21 mM sodium citrate; and

(2) [[15% or higher in the presence of 16 mM magnesium sulfate]] a residual activity in the presence of 16 mM magnesium sulfate that is:

(i) higher than the residual activity in the presence of 16 mM magnesium sulfate of a corresponding *Limulus polyphemus* Factor C protein expressed in Sf9 as a host cell, or

(ii) higher than the residual activity in the presence of 16 mM magnesium sulfate of a native *Limulus polyphemus* Factor C protein,

wherein the horseshoe crab Factor C protein is not a horseshoe crab Factor C protein having less than 15% residual activity in the presence of 16 mM magnesium sulfate.