

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 REPLY TO PATENT OWNER'S RESPONSE

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LISTING OF EXHIBITS

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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.

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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.
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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

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1049	RESERVED
1050	U.S. Appln. No.: 16/331,810, “Recombinant Proteins Derived From Genus Limulus, 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
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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

“The written description requirement is not satisfied by what *could have* been disclosed, but was not.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013, 1022 (Fed. Cir. 2002). The crux of Patent Owner’s (“PO’s”) argument on written description in this case is that its inventors *could have* disclosed the coding sequences for *Limulus polyphemus* Factor C in their specification, even though they did not. That argument fails as a matter of law.

It is undisputed that neither the cDNA nor the amino acid sequences encoding the coagulation cascade zymogen proteins (Factor C, Factor B, and Pro-clotting enzyme) from the horseshoe crab species *L. polyphemus* appear in challenged claim 21’s alleged priority documents (’767 Application), dated December 10, 2013. *See generally*, EX1006. It is also undisputed that such sequences were not published or made publicly available (by the inventors or anyone else) as of that date. EX2038, ¶35.

In view of this, PO argues that it would have been within the knowledge and skill of a POSA to work to construct the *Limulus polyphemus* sequence information from bulk horseshoe crab sequence data deposited at NCBI even though the inventors also undisputedly did not reference, or incorporate into their priority document, or apparently even know about, that data. To this end, PO supplements the priority document with an extraordinary amount of extrinsic

record gap-filling, detailing the elaborate protocol a POSA *could have* followed in October of 2013 to ascertain the Factor C cDNA and amino acid sequences from information purportedly available in the NCBI database at that point. PO's supplementation only highlights the clear deficiency of its priority document—where this information was necessary in order for the inventors to claim entitlement to its filing date. Even using present-day tools, however, PO's expert did not construct and report the entire *Limulus polyphemus* Factor C coding sequence. *See generally*, EX1038, *see also id.*, ¶¶64.

PO's hindsight-driven reliance on the post hoc work of a POSA also fails because while “[t]he knowledge of ordinary artisans may be used to inform what is actually in the specification, [it cannot] teach limitations that are not in the specification, even if those limitations would be rendered obvious by the disclosure in the specification.” *Rivera v. Int’l Trade Comm’n*, 857 F.3d 1315, 1322-23 (Fed. Cir. 2017). Though PO insists a POSA *could have* derived the required sequences that are nowhere mentioned in the priority document, two of the three named inventors of that claim admitted three years later—in an unrelated patent filing claiming recombinant *Limulus polyphemus* zymogen proteins—that only *then* (in 2016) had they discovered it. EX1005, ¶¶0009-0017.

But claim 21 isn't just to the *Limulus polyphemus* Factor C sequence. It requires HEK293 recombinantly produced Factor C proteins from *Limulus*

polyphemus horseshoe crabs, **and also** requires such proteins to demonstrate a particular enzymatic activity—a residual activity in the presence of specific concentrations of ions—across an exceedingly wide and unsupported range. So setting aside whether the sequences could have been obtained, the ’767 Application says **nothing** about the residual activity of the claimed recombinantly produced *Limulus polyphemus* Factor C proteins or how to make or use them. So PO must again resort to reliance on a POSA’s purported ability to predict—from the behavior of unclaimed species of proteins—the residual activity of the claimed *Limulus polyphemus* recombinant Factor C.

PO argues relies on purported evidence that the **gross** function of native Factor C in the coagulation cascade was thought to be overlapping between the four extant species of horseshoe crabs (i.e., Factor C functions similarly in the presence of Factor B and Pro-clotting enzyme to detect endotoxin). However, it was also known that the particular and **specific** enzymatic activity of such proteins (i.e., narrower measures of function in particular environments) exhibited significant variation across different assays, from which comparative conclusions between species could not be made. Indeed, many of PO’s cited references—offered to establish a percentage of sequence similarity between species—actually show **differences** in the specific assay activity of native *Limulus polyphemus* Factor C when compared with proteins of other species. The inventors themselves

also established that recombinantly produced Factor C proteins exhibit significantly different residual activities from their native counterparts in unpredictable ways. EX1006, FIG. 7. These differences preclude identification of any common structural feature driving the claimed Factor C function which, alongside the absence of any specific example within the scope of the claim, renders the '767 Application's description insufficient as a matter of law. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc).

Because claim 21 is not entitled to a December 10, 2013 priority date, or any date earlier than its April 30, 2019 actual filing date, it is obvious over the interim prior art reference Mizumura in combination with either the '498 PCT or McClymont.

II. PO'S CONTENTION THAT SEQUENCING *L. POLYPHEMUS* FACTOR C WAS "ROUTINE" IS UNDERMINED BY ITS OWN ARGUMENTS

In ***October of 2016***, PO and two of the three inventors of challenged claim 21 told WIPO and others that they had ***invented*** recombinant *Limulus polyphemus* Factor C having finally determined the cDNA and amino acid sequences of that protein for that species. EX1005, ¶0009 ("all of [the prior art] methods use recombinant proteins derived from organisms of the genus *Tachypleus*. There have been no reports of a reagent using recombinant proteins derived from *Limulus polyphemus*...the reason is that in *Limulus polyphemus*, the proteins and their

genes involved in the mechanism of coagulation caused by endotoxin ***have not been completely identified structurally or functionally.***” EX1005, ¶¶0009-10.¹ The inventors reference available bulk sequence data (***much like PO relies on today***) but described “the difficulty in accurately determining the full-length sequence structures of these proteins and genes in *Limulus polyphemus*.” *Id.*, ¶¶0012-0013.

But in 2016, the inventors reported that:

The present inventors have succeeded in obtaining full-length cDNAs encoding all of the protein factors involved in the coagulation mechanism of *Limulus polyphemus*, ***something that no one had succeeded in doing for many years, and in expressing all of the recombinant proteins...thereby completing the present invention.***

Id., ¶0017.

PO tells the Board, today, that constructing and expressing the *Limulus polyphemus* Factor C coding sequences in 2013 was “routine,” ***after*** having filed for a patent in the U.S., and secured and (just recently) saved a patent in Europe,²

¹ Emphasis added and internal citations omitted unless otherwise noted

² The EPO maintained PO’s claim to recombinant *Limulus polyphemus* Factor C protein (EX1068, 196:18-198:17) with a priority date of October 18, 2016 based on PO’s insistence that such claim was not obvious over the same disclosure as the

based on the inventors' vehement representations that in 2016: "***it [had] not been possible*** to accurately determine the full-length sequence ***structure, expression, and function of these proteins.***" EX1005, ¶0012.³

The inventors' stated struggles to obtain and express the cDNA and amino acid sequences for the *Limulus polyphemus* zymogen proteins (including Factor C) are consistent with contemporaneous research by Karen McClymont, who wrote in 2017 that "The sequence of *Limulus polyphemus* Factor C is not publicly available. For this reason, it was necessary to assemble the lpFC gene from the raw data...in order to synthesise full-length lpFC." EX1010, 36.

'767 Application and arguments including that an LpFC sequence alignment provided "an alignment of a ***previously unknown*** sequence" as of October 18, 2016. EX1043, ¶¶ 56-57. *In re 318 Patent Infringement Litig.*, 578 F. Supp. 2d 711, 736-37 (D. Del. 2008) (claims cannot be both non-obvious over the prior art and enabled by that same art).

³ Petitioner will separately pursue an appropriate remedy against PO under §42.11(d)(2).

McClymont⁴ explained that even as of 2017, “there are *known variances between different LPS binding sites*, [so] it is beneficial to study lpFC to identify any differences that may arise between the species in terms of sensitivity or specificity of binding.” EX1010, 36; *see also id.*, 38. She also described challenges with generating the Factor C sequence: “As a result of *failing to produce* a sensible construct, the contigs identified in the tblastn search were assembled using the ttFC cDNA sequence as a guide.” *Id.*, at 42. *See Bos. Sci. Corp. v. Johnson & Johnson Inc.*, 647 F.3d 1353, 1366, (Fed. Cir. 2011) (no written description—a patentee may only rely on information that is “‘*well-known in the art*’ for purposes of meeting the written description requirement.”).

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

To the extent PO suggests otherwise, 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. All agree that background and experience

⁴ McClymont was a Ph.D. student but counseled by more experienced scientists.

EX1010, 1.

qualify a POSA rather than specific degree or educational focus. EX1069, 44:19-46:8; EX1067 27:16-28:11. And in any case, PO’s expert conceded that his opinions do not change depending on which POSA definition is used. *Id.* 33:7-11.

IV. RECOMBINANT *LIMULUS* FACTOR C PROTEINS WITH RESIDUAL ACTIVITY ACROSS THE BROADLY CLAIMED FUNCTIONAL RANGE ARE NOT DESCRIBED

A. The Coding Sequences For *Limulus Polyphemus* Factor C Are Not Described And Were Not Published Until Well After 2013

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 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 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 (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 its publication date. EX1067, 95:3-96:14.

Moreover, despite walking through pages of experimental protocols that a POSA "would have" followed to assemble the *Limulus* Factor C sequence from the bulk horseshoe crab genome data available at the noted website, Dr. Schaefer did not actually construct it. 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 of the sequences provided by the inventors ***in the 2016-filed '498 PCT to work backward. Id.***, 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 an array of research experiments a

POSA *could try* (and still no constructed sequence) is inadequate to satisfy the written description requirement.

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 POSAs, less detail was required in the specification. The Court explained, "Brita's reliance on the knowledge of persons of ordinary skill is similarly unavailing," and rejected Brita's argument that because other non-carbon-block filter media types were known to POSAs the patents detailed description of carbon-block embodiments sufficed to show possession of the full scope of the claim. *Id.*, at 1336.

As with the "residual activity" aspect of claim 21, patentee Brita sought to extrapolate a POSAs understanding of the claimed "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 FRAP value—"What Brita overlooks is that in the context of the FRAP equation (itself previously unknown), the ultimate effect of adjusting known variables was far from certain...[and was] unpredictable due to the interrelatedness of variables." *Id.* The Court ruled, "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 cannot “make up for” the absence of disclosure of recombinantly produced *Limulus polyphemus* Factor C and *extrapolate* that protein's claimed residual activity function based on information about other species of horseshoe crab (where, as here, many variables are implicated).

B. Differences In Sequence and Function Preclude Identification of Structure Common to the Claimed Proteins

Using the 2016-reported *Limulus polyphemus* sequence, PO's expert compared it to the sequence for other species 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. But Dr. Schaefer didn't know if a POSA would “pay any attention at all to

what the inventors call out as being conserved versus nonconserved” in any case.

EX1067, 118:17-119:7. 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*, 598 F.3d at 1351. Instead, PO’s strategy is to ignore the statements of the inventors (both later in time and in the ’767 Application) in favor of filling gaping holes in the priority document with hindsight-driven protocols that other POSAs could have obviously tried.

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 didn’t account for them. EX1067, 119:11-120:5 (dismissing a nonconservative mutation in a functional domain of Factor C as having 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 hand-waves about the lack of required “structural features” common to the claims but fails to offer any such features. POR, 25-27. 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 simply 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. *Ariad*, 598 F.3d at 1350; *Duke Univ. v. Sandoz Inc.*, 160 F.4th 1305, 1311 (Fed. Cir. 2025).

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

Despite claiming functionally, 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 on the “residual activity” metric in horseshoe crab 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. Instead, various studies prior to 2013 confirmed that in the context of specific assays, different Factor C proteins behaved *differently*.

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*.⁵ However, the ’432 Publication reports “the 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., below) while the highest

⁵ Tryptic peptide sequencing is an incomplete assessment of sequence identification. EX1067, 150:25-151:20.

enhancement 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, below).

FIG. 1.

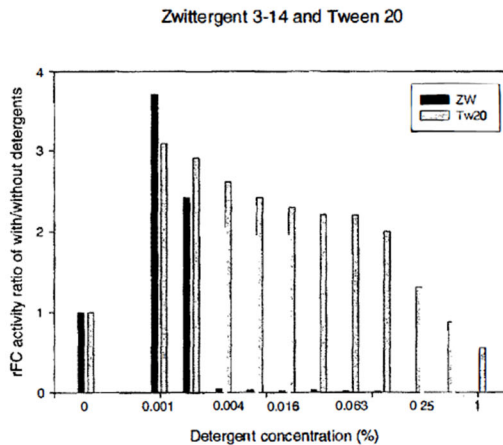
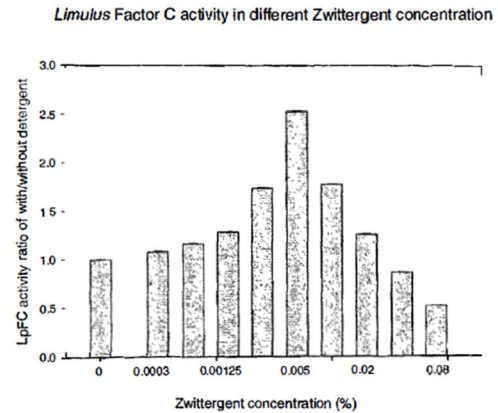


FIG. 6



The '432 Publication provides no explanation for this difference, and Dr. Schaefer resisted comparisons, but acknowledged that a POSA would also not be able to use the '432 Publication data 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 the specific metric of residual activity. *Id.*

Similarly, in Loverock (EX2049), the authors compared endotoxin detection ability between recombinant FcCc (*Carcinoscorpius*) 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 revealed that “the rFC mean response was significantly different from the two LAL-based procedures.”

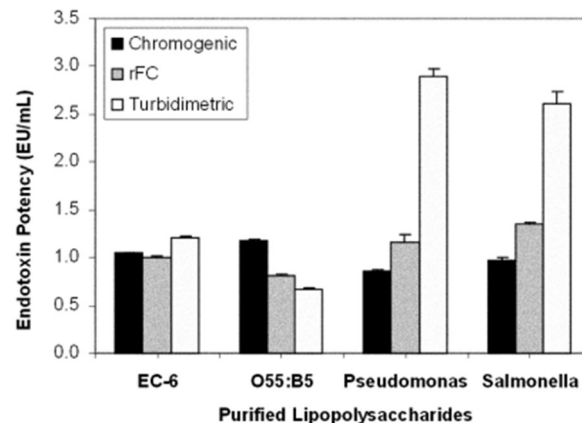


Figure 3. Endotoxin response to different source materials.

EX2049, 4, 5. Dr. Schaefer, who cited Loverock, concurred that 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 new recombinantly-produced protein (from *Limulus polyphemus*) based on the reported residual activity of an entirely different species of protein.

PO's cited reference—Alwis—reported assay result differences between *Limulus polyphemus* Factor C proteins and recombinantly-produced *Carcinoscorpius rotundicuada* Factor C. EX2036, Abstract, 3.⁶ The authors attributed these differences in function to the 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. Shaefer dismissed the author's explanation (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 result differences across different species of horseshoe crab. None of the '432 Publication nor Loverock nor Alwis say anything about the claimed “residual activity” metric, specifically,

⁶ Dr. Shaefer dismissed these differences as potentially attributable to a “universe of possibilities for why they got different results.” EX1067, 164:13-167:4. *See also*, EX1069, 58:7-59:6 (“The interference and interaction that occurs in such assays is multifactorial and very difficult to attribute to a...single origin.”).

Finally, Tokunaga (EX1022), cited at length by PO, does not discuss “residual activity” or recombinant Factor C proteins. Tokunaga does, however, reveal specific and important amino acid *differences* between even 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. Regarding 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, 147:1-9.

Moreover, because the inventors 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 reluctant to extrapolate similarities in gross function to more nuanced functional properties under particular assay conditions for recombinantly produced Factor C in mammalian cell lines across *different* species of horseshoe crabs. Dr. Shaefer 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 21. *Lockwood*, 107 at 1572; *see also In re Kuenzel*, Appeal 2009-015373, 2011 WL 938717, at *5 (B.P.A.I. Mar. 17, 2011).

D. There Were Still Questions About The Mechanism Of Action of Factor C Well After 2013

PO alleges that by 2013, much about the function and activity of Factor C was characterized and was understood to be identical across horseshoe crab species. POR, 21-24. But this narrative is refuted by McClymont's 2017 summary of the state of the art, where she states, "The recognition of the lipid A component of LPS by Factor C is very specific, and details surrounding this type of interaction *are lacking...Contradictory results* as to the location of the LPS-binding site have been published by Tan et al. and Koshiba et al. after both groups carried out experiments on different fragments of Factor C." EX1010, 32. Dr. McClymont's research was thus based on elucidating *more* information about Factor C binding characteristics in view of open questions and then-conflicting research on the exact

mechanism of LPS binding. *Id.*, 35. PO’s contention that the function of Factor C was fully “characterized” prior to 2013 is baseless. EX2038, ¶35.

V. THE EXPERIMENTATION REQUIRED TO PRACTICE CLAIM 21’S FULL SCOPE UNDUE.

Claim 21—with unbounded upper ranges for residual activity in either of two ionic solution options—is undisputedly broad. EX1069, 108:9-109:8, 64:14-65:14, 66:8-19; EX1067, 202:11-203:16. And yet, 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 within 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.

Such open-ended claims—with no description of achieving the higher values and no explanation for how to do so by December 10, 2013—fail the enablement requirement. *MagSil Corp. v. Hitachi Glob. Storage Techs., 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); *see also Epistar Corp. v. Lowes Cos., Inc.*, 2020 WL 771096, at*6-8 (C.D. Cal. Feb. 11, 2020).

PO relies on the EPO testimony of Dr. Frohman regarding that expert's assertion of how to elucidate the sequence information for *Limulus polyphemus* as of 2016. POR, 37-41. But not only is Dr. Frohman's testimony directed to a time period three years later than the claimed priority date, Dr. Frohman says ***absolutely nothing*** about the residual activity of any Factor C protein (recombinantly produced or otherwise). And, as discussed above (section IV.C, D., *supra*), the alleged gross-level functional similarity of zymogen proteins across species of horseshoe crabs was accompanied by evidence of specific ***differences*** in enzymatic activity in specific assays. In view of these differences, a POSA would not have simply assumed without experimentation that if he or she ***could*** elucidate the coding sequence for *Limulus polyphemus* Factor C and ***could*** recombinantly produce such proteins in HEK293 cells (which no one had ever actually done by December 10, 2013), that the resulting residual activity of such proteins was going to align with that of other species across the full scope of claim 21. EX1002, ¶¶119-146. PO's enablement argument does not satisfy §112. *Brita*, 156 F.4th at 1336-39; EX1065, 189:8-18.

VI. BY APRIL 30, 2019 CLAIM 21 WAS OBVIOUS OVER THE PRIOR ART

If claim 21 is found neither described nor enabled by December 10, 2013, PO has not argued for any interim priority date and the Board should assess

patentability as of the actual filing date of claim 21 (April 30, 2019). In that case, there is no dispute that Mizumura and the '498 PCT are prior art. POR, 44.

A. The Obviousness of Claim 21 By 2019 Is Not Inconsistent With That Claim Lacking §112 Support As of December 10, 2013.

PO does not argue that the combined teachings of Mizumura and the '498 PCT fail to disclose all of the limitations of claim 21, but only that combining the prior art teachings would “directly contradict[] Petitioner’s and its expert’s arguments” regarding written description and enablement. POR, 45-46. Not so.

As of December 10, 2013, for all of the reasons discussed in Section IV, *supra*, and the Petition, Section IX.B., the full scope of claim 21 was neither described nor enabled. As Dr. Jain testified, however, by April 30, 2019, a POSA reading Mizumura’s reports on residual activity in *Tachypleus tridentatus* Factor C and having access to the then-published sequence information for *Limulus polyphemus* Factor C and the experimental results of the '498 PCT would have found it obvious to try to generate an example of a HEK293-recombinantly produced *Limulus polyphemus* Factor C protein and would have reasonably expected that protein to ***fall within*** the claimed residual activity range. EX1002, ¶¶156-192.

Because the enablement and written description look to the full scope of the claim, it is possible that the prior art renders an embodiment that falls within the scope of the claim obvious, while that prior art (viewed with the teachings of the

patent) do not enable or describe the full scope of the claim. There is no inconsistency. *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1374 (Fed. Cir. 2023) (precedential); *In re Mraz*, 455 F.2d 1069, 1072-73 (CCPA 1972); *Pharm. Res., Inc. v. Roxane Lab'ys, Inc.*, No. 03-3357, 2006 WL 3231427, at *16 (D.N.J. Nov. 8, 2006).

B. The Petition Demonstrates That A POSA Would Have Had A Reasonable Expectation of Success In Generating An Exemplary Protein of Claim 21.

PO argues that there is insufficient evidence of a reasonable expectation of success as to Ground 1, arguing that its own inventor declaration was “conclusory.” POR, 46-48. But the Petition relied on 2018 testimony from Dr. Mizumura that because of his comparison between the newly-reported *Limulus polyphemus* sequence and that of prior sequenced species, “a [POSA] would readily recognize that the presently claimed invention could also work when Factor C is the Factor C of *Limulus Polyphemus*.” EX1029, 2-5. The Petition explains that this testimony from the inventor *in combination with* the successful expression of *Limulus polyphemus* Factor C documented in the '498 PCT and Mizumura's residual activity results would have given a POSA a reasonable expectation of success in achieving an *exemplary* Factor C protein of claim 21. Pet. 57-60, citing EX1005, ¶¶155-185, 205-206, 282-290; EX1002, ¶¶179-187.

Such evidence is more than adequate to establish a POSA's reasonable expectation.

C. Mizumura In View of McClymont Also Renders Claim 21 Obvious As of April 30, 2019.

PO offers no independent criticism of Ground 2 beyond the same criticism of its inventor declaration discussed above. POR, 48-49. A POSA considering McClymont would have had the same 2018 sworn testimony from Dr. Mizumura regarding the sequence comparison and likelihood that *Limulus polyhemus* Factor C would work and Mizumura's residual activity results and so would have reasonably expected such expressed proteins to have a residual activity falling in the claimed range. Pet. 57-61.

D. PO's Purported Evidence of Secondary Considerations Is Flawed And Legally Insufficient.

PO cites nothing more than data presented in an August 11, 2021 Declaration submitted by Dr. Mizumura ("Mizumura Declaration") and a post-priority document (D19) (both when compared to FIG. 7 of Mizumura). Neither piece of evidence saves claim 21.

1. The Mizumura Declaration Is Insufficient To Demonstrate Unexpected Results of Claim 21 For At Least Four Reasons.

First, the data in the Mizumura Declaration is from proteins of *Limulus polyphemus* Factor C recombinantly produced in **CHO DG44 cells**. Because claim 21 requires such proteins to be produced in HEK293 cells, the data in the

Mizumura Declaration is outside the scope of—and therefore irrelevant to—the performance of the claimed invention. EX1069, 115:1-8.

Second, the data in Mizumura FIG. 7 shows that PO's closest prior art *also satisfies* the claimed residual activity range such that there is no difference between the prior art and the invention when viewed through the exceedingly broad scope of claim 21. *See* EX1006, FIG. 7 (showing that *Tachypleus tridentatus* expressed in HEK293 cells yields values of 20-25% residual activity in magnesium sulfate and values of about 20-30% residual activity in sodium citrate, both of which fall within the ranges of claim 21); EX1069, 120:9-121:17.

Third, the comparison between proteins shown in the data cited by Dr. Morris is clouded by a host of uncontrolled variables that make it difficult to conclude that differences in residual activity are attributable solely to the claimed features. Dr. Morris agrees. EX1069, 88:12-91:8; *see also id.*, 91:9-98:1, 105:8-106:14, 131:5-136:19.

Finally, the comparison between the Mizumura Declaration data and Mizumura FIG. 7 demonstrates that for *at least half* of the scope of claim 21 (residual activity in sodium citrate), there is essentially *no difference* between PO's data and the closest prior art. *Compare* EX2042, ¶43, column 5, *with* ¶46, column 5, *or compare* ¶44, “approximately 20-30% in HEK293 cells” under “21 mM sodium citrate”, *with* ¶47, “just under 25% in 21 mM sodium citrate”; *see also*

EX1069, 118:17-119:20; 152:12-154:11. In view of this similarity, there cannot be unexpected results commensurate with the scope of claim 21.

2. D19's Data is Unverified And Can't Be Compared With Unclaimed Proteins To Establish Unexpectedness

The only other evidence of unexpected results provided by PO is a document submitted during prosecution of the '318 Patent ("D19").

PO's expert published and testified to the accuracy of the statement that "[m]inor differences in procedure (temperature, mixing time and operators) result in significant variation [in function] even when the same LAL method is used on the same samples at the same time in the same laboratory." EX2062, 605; *see also* EX1069, 125:3-127:16. She also testified to the increased weight placed on the reliability of consistency across laboratories when making comparisons about assay results. EX1069, 79:5-82:6; 129:6-21, 151:25-152:21. She then conceded to a myriad of unknowns with respect to the D19 data and a myriad of differences between that data and FIG. 7 of Mizumura. EX1069, 155:5-157:16, 157:18-159:18, 160:6-11, 161:3-165:5, 166:21-167:3, 167:14-20, 168:17-171:9. Dr. Morris's opinions about the heavily confounded D19 data comparison should be given no weight.

VII. CONCLUSION

Claim 21 is unpatentable as obvious.

Respectfully submitted,

Date: 3/2/2026

/Chelsea A. Loughran/

Chelsea a. Loughran, admitted *pro hac vice*
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing **PETITIONER'S REPLY TO PO'S RESPONSE** contains 5,596 words excluding; a table of contents, a table of authorities, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: March 2, 2026

/MacAulay Rush/
MacAulay Rush
Paralegal
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:

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