

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. PGR2025-00023
Patent No. 11,959,109

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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1001	U.S. Patent No. 11,959,109
1002	Prosecution History of U.S. Patent No. 11,959,109 (Application No. 18/346,420)
1003	Declaration of Siddhartha Jain, Ph.D., PMP (“Jain”)
1004	Curriculum Vitae of Dr. Siddhartha Jain, Ph.D., PMP
1005	International Patent Publication No. WO 2018/074498 A1
1006	Higdon 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.
1007	Kobayashi et al., “Factor B Is the Second Lipopolysaccharide-binding Protease Zymogen in the Horseshoe Crab Coagulation Cascade,” <i>J Biol Chem.</i> 2015 Jun 24; 290(31):19379–19386.
1008	Japanese Priority Application No. JP2012-269840 (certified translation)
1009	U.S. Patent No. 5,716,834
1010	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.
1011	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
1012	U.S. Patent Application Publication No. 2021/0363564
1013	Declaration of Dr. Mary K. Bolin
1014	RESERVED
1015	U.S. Patent Application Publication No. 2019/0241629
1016	U.S. Patent Application Publication No. 2015/0307864
1017	U.S. Patent Application No. 14/650,767, as filed June 9, 2015
1018	RESERVED
1019	Shi et al., “Protein N-Glycosylation in the Baculovirus-Insect Cell System,” <i>Curr Drug Targets.</i> 2007 Oct; 8(10): 1116–1125.
1020	RESERVED
1021	RESERVED
1022	Transition Certification for U.S. Patent Application No. 15/983,725, filed May 31, 2019.

1023	RESERVED
1024	RESERVED
1025	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.
1026	Dwarakanath, R.S. et al., “Recombinant COS-1 cells express <i>Carcinoscorpius rotundicauda</i> Factor C,” <i>Biotechnology Letters</i> . 1997 April; 19(4):357-61.
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	RESERVED
1029	RESERVED
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	RESERVED
1033	RESERVED
1034	RESERVED
1035	RESERVED
1036	RESERVED
1037	RESERVED
1038	Sekiguchi, K. and Shuster, C.N., “Limits on the Global Distribution of Horseshoe Crabs (<i>Limulacea</i>): Lessons Learned from Two Lifetimes of Observations: Asia and America,” <i>Biology and Conservation of Horseshoe Crabs</i> , 2009.
1039	Hossler et al., “Optimal and consistent protein glycosylation in mammalian cell culture,” <i>Glycobiology</i> . 2009 Sep; 19(9):936-4.
1040	File History of United States Application No. 16/399,386
1041	ExpiCHO™ Expression System - USER GUIDE – For transfection of ExpiCHO-S™ in a defined, serum-free medium. Catalog Number A29133, Publication Number MAN0014337 Revision D.0 (May 25, 2018).

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
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	RESERVED
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	RESERVED
1055	RESERVED
1056	U.S. Appln. No.: 18/346,420, “Novel Recombinant Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Non-Final Office Action, Sept. 15, 2023
1057	R. Davis, Acting USPTO Leader Says New Policies Will Bolster Patents, Law360 (Apr. 1, 2025), https://www.law360.com/articles/2316863/ (accessed June 10, 2025)

1058	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Preliminary Amendment, Jun. 9, 2015
1059	U.S. Patent No. 10,144,923
1060	U.S. Patent No. 10,982,202
1061	U.S. Patent No. 6,391,570
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 Surveillance 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	U.S. Patent 11,499,177

I. INTRODUCTION

Claims 1-9 of the '109 Patent lack written description or enabling disclosure and so are not entitled to the December 10, 2013 priority date. Patent Owner (“PO”) does not argue for any interim priority date and so if deprived of the 2013 date, claims 1-9 are entitled to an effective filing date of no earlier than their actual filing date of July 3, 2023. When afforded this priority date, claims 1-9 are anticipated by the intervening prior art.

Written description is “not a question of whether one skilled in the art *might* be able to construct the patentee’s device from the teachings of the disclosure.... Rather, it is a question whether the application necessarily discloses that particular device.” *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987). Likewise, “the [enablement] inquiry is not whether it was, or is, *possible* to make the full scope of the claimed device...[t]he inquiry is whether the patent’s specification *taught* one of skill in the art how to make such a device without undue experimentation as of the patent’s effective filing date.” *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018).

In its Response, PO repeatedly foists the burden on Petitioner of demonstrating that a POSA *could not* accomplish the full scope of what is required by the challenged claims (aided by extrinsic materials found nowhere in its specification). POR, 68, 70. But it is PO who has failed to meet its burden to

establish written description and enablement of the challenged claims by demonstrating that all of the information undisputedly ***not found*** in the '767 Application that PO relies on was well-known and conventional background information otherwise unnecessary to the priority document. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1992). PO has plainly failed to make this demonstration. At best PO demonstrates that the missing disclosures were technically possible and obvious for a POSA to arrive at, while simultaneously seeking patents on the same missing disclosures years later, alongside uninterested parties also claiming that aspects of the missing disclosures were advancements. On this record, PO's argument fails.

By way of example, claim 1 broadly covers the expression of the Factor B protein and Pro-clotting enzyme from ***all species*** of horseshoe crab, in ***all mammalian expression systems*** and requires such proteins to work (i.e., have their activity in the horseshoe crab coagulation cascade). EX1001, cl. 1. It is undisputed that the '767 Application does not describe or disclose how to make and use the claimed Factor B or Pro-clotting enzyme from ***any*** horseshoe crab species in ***any*** mammalian expression system. **Not a single one.** POR, 40.

Without any specific description in the '767 Application of these proteins, PO must rely on the leaps and "predictions" a POSA would make from what is described in the '767 Application (expression of these proteins from *Tachypleus tridentatus* in

insect cells, or expression of Factor C in two mammalian cell lines) to what is actually claimed. But the Petition establishes that such open-ended research assignments are repugnant to the PO's disclosure obligations. The inventors themselves described (and relied heavily on during prosecution) the **challenges** of expression of Factor C in insect cells (suppression of function of the resulting protein in ions) and described scientists' inability to express functional Factor C protein in the COS-1 mammalian expression system. EX1017, ¶¶0010-11; EX1002, 125-26 ("Earlier attempts in our lab to express rFC in E. coli, yeast and mammalian cells...may not have met the requirements for Factor C folding and modification."). And other publications, including those cited by PO, explain the challenges of using mammalian expression systems to make proteins. EX2110, 7 ("Mammalian systems do have some drawbacks as follows. (i) Poor secretion.").

Petitioner's expert, who has decades of experience working with complex proteins, testified that recombinant protein expression is a challenging undertaking that is sensitive to protein sequence differences where a POSA would not simply assume because one protein (*Tachypleus tridentatus* Factor C) was successfully expressed in a mammalian system, that **different proteins** (Factor B, Pro-clotting enzyme), from different species of horseshoe crab (*Limulus polyphemus*, *Carcinoscorpius rotundicuada*, *Tachypleus gigas*, none of which had even been sequenced) would also be successfully expressed in the full scope of mammalian

systems claimed. EX1003, ¶¶59-68, 71-74, 89-92, 96-98, 101-112, 118-121; EX1065, 82:3-8, 132:1-20, 138:11-139:3, 143:16-144:8, 146:11-147:1, 161:4-16.

Could a POSA *eventually* accomplish this with the passage of time from the original priority date and advanced, additional guidance? Maybe. But as the record demonstrates, it would require later research and experimentation. PO's post-hoc rationalization turns the patent bargain on its head. The record demonstrates that, in fact, it took the inventors three years to accomplish most of this work, which they reported in their 2016 unrelated patent application. EX1005, ¶¶0178-180 (“[T]here was *success for the first time in expressing and obtaining* a protein from *Limulus polyphemus* that may have factor C activity...factor B activity...[and] pro-clotting activity”). And this is just an example. Claim 1 is broader in a myriad of other ways that are not described or enabled and that would require additional experimentation to complete (e.g., expression of proteins from “the same or different” mammalian systems that all have their “activity”).

The '109 Patent inventors over-claimed technology not in their possession, failing to describe a single example of how to make and use the full scope of these claims. They now argue that leaving years of research and significant effort to POSAs to arrive at such claim scope comports with U.S. patent law written description and enablement standards. This argument fails.

PO is not entitled to the December 10, 2013 priority date. Instead, challenged claims 1-9 are entitled to an earliest effective filing date of no earlier than July 3, 2023 and with this date, those claims are undisputedly anticipated by the '629 Publication.

II. PERSON OF ORDINARY SKILL IN THE ART

To the extent PO argues otherwise, Dr. Jain has over 18 years of experience in expressing and characterizing recombinant proteins with significant experience in different formats of endotoxin assays, and ample other relevant experience. EX1003, ¶2; EX1065, 55:22-56:1, 57:6-8, 58:11-13, 59:2-4, 49:20-50:9, 50:12-19, 49:4-6, 63:14-20. He is unquestionably a POSA as of 2013.

PO's expert conceded that his opinions do not change depending on which POSA definition is used. EX1067, 33:7-11. Under either of the Parties' POSA definitions, Dr. Jain is qualified and the challenged claims are unpatentable. *See Unified Patents, Inc. v. Ideahub, Inc.*, IPR2020-01338, Paper 48, 12-13 (Feb. 7, 2022).

III. PATENT OWNER HAS ARGUED THAT SEQUENCING AND EXPRESSING *L. POLYPHEMUS* FACTOR C, FACTOR B, AND PRO-CLOTTING ENZYME WAS NOT "ROUTINE" IN 2016

In *October of 2016*, PO and two of the three named inventors of challenged claim 21 told WIPO and others that they had *invented* recombinant *Limulus polyphemus* Factor C, Factor B, and Pro-clotting enzyme, having finally

determined the cDNA and amino acid sequences of those proteins for that species of horseshoe crab. EX1005, ¶0009-10 (“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*, which is widely used as a lysate reagent...[t]he 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.***”)¹

The inventors reference available bulk sequence data (***much like PO relies on today***) but reported on “the difficulty in accurately determining the full-length sequence structures of these proteins and genes in *Limulus polyphemus*.” *Id.*, ¶¶0012-13, 17.

Relevant to the challenged claims, the inventors stated unequivocally in 2016 “***there was success for the first time*** in expressing and obtaining a protein from *Limulus polyphemus* that may have factor C activity...factor B activity...[and] pro-clotting enzyme activity.” EX1005, ¶0180.

PO tells the Board, today, that constructing the *Limulus polyphemus* protein coding sequences for Factors C, B, and Pro-clotting enzyme and expressing them

¹ Emphasis added and internal citations omitted unless noted.

in 2013 was “routine.” But this is after having filed for a patent in the U.S., and secured and (just recently) saved a patent in Europe,² 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 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.

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 art with the same disclosure as the ’767 Application and after PO argued *inter alia* that an LpFC sequence alignment provided “an alignment of a previously *unknown sequence*” as 2016. EX1043, ¶¶ 56-57. PO cannot have it both ways. *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 same art).

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

For this reason, it was necessary to assemble the lpFC gene from the raw data.”

EX1011, 36. 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.” *Id.*, at 36; *see also id.*, at 38. She also

described failures in 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 ...written description.”).

IV. CLAIM CONSTRUCTION

The plain meaning of the terms in the challenged claims require (both in the

claim and as explained in the specification) that the three component proteins

(Factor C, Factor B, and Pro-clotting enzyme) have their “activity”, which the ’109

Patent defines as being the ***function*** of that particular protein in the presence of the

other cascade members: “The ***activity of Factor C*** refers to such an activity that the

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

EX1010, 1.

Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B. EX1001, 15:64-16:9, 21:3-16 (parallel language for Factor B), 21:31-53 (parallel language for Pro-clotting enzyme).

This appears to be undisputed. Dr. Schaefer agreed that the claimed “endotoxin assay agent” is something that could be used in an endotoxin assay, and that has all of Factors B, C, and Pro-Clotting enzyme, where all of these proteins have the ability to function as they would in the zymogen clotting cascade reaction.⁵ EX1068, 232:21-243:18; *see also*, EX1001, 20:7-19.

Dr. Schaefer’s definitions of “activity of Factor B” and “activity of Pro-clotting enzyme” are even ***broader*** than those set forth in the ’109 Patent specification as also including the scenarios where each protein is activated not only by the upstream activated protein, but by “any protease known to activate” that protein. *See, e.g.*, EX1068, 239:13-18, 242:7-243:8.

PO opposes the idea that claim 1 of the ’109 Patent ***requires*** the assay agent to be used in a cascade (POR, 24), arguing that the claimed method could be for producing each component separately. This is illogical in view of the limitation of “producing” the assay agent comprising these components which are designed to

⁵ Dr. Schaefer agrees that Factors B, C, and Pro-clotting enzyme operating in the coagulation cascade all have their claimed “activity”. EX1068, 256:25-257:24.

work together to detect endotoxin. EX1017, FIGS. 4, 5, ¶0044. In any case, it is a red herring, because Petitioner does not limit the claim in this manner. The challenged claims cover a range of embodiments so long as in all cases, the recombinantly expressed proteins demonstrate their function to detect endotoxin and either cleave a substrate (as with Factor C) or drive the next step in the coagulation cascade.⁶ However, the '767 Application fails to describe or enable the full scope of such exceedingly broad claims. Pet., 9-11, 23-60.

V. THE '629 PUBLICATION ANTICIPATES CLAIMS 1-9

If the Board finds that claims 1-9 were not described or enabled by the '767 Application in December 10, 2013, PO has not argued for any interim priority date (POR, 1, 30) and the Board should assess patentability as of the actual filing date of those claims (July 3, 2023). There is no dispute that the '629 Publication is prior art to claims 1-9 if those claims are entitled only to their actual filing date.

⁶ PO concedes this point with its chart on pages 25-27 of the POR. Claim 1 is silent as to the extra limitation of claim 10. It *encompasses* the claimed assay agent capable of working as in the coagulation cascade, but is also broader. EX1068, 256:13-14 (“Claim 10 has additional steps that are not included in claim 1.”).

PO does not dispute that if the '629 Publication is prior art to claims 1-9, it discloses every limitation of challenged claims 1-9, and therefore anticipates them. PO offers no argument or evidence to the contrary. *See generally* Paper No. 26.

A. Claim 1 Is Not Described In The Four Corners of the '767 Application

PO breaks up the claim and points to examples of certain parts (or near-examples of such parts) or fills in undisclosed parts based on the purported work and hindsight efforts of a POSA, and then concludes that description of these component pieces satisfies § 112 for the claimed invention. *See, e.g.*, POR, 36-37, 37-38. This is a misapplication of written description law. The challenged claims must be described in the '767 Application, in a manner sufficient to demonstrate possession of the full scope of the invention *as a whole*. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346-48 (Fed. Cir. 2013) (no written description—"Taking each claim—as we must—as an integrated whole rather than as a collection of independent limitations, one searches the 2000 application in vain for the disclosure of even a single species that falls within the claims.").

The purported invention of challenged claim 1 is an endotoxin assay agent comprising a series of components, all of which are functionally able to play their part in the coagulation cascade (whether that is actually in the functioning cascade (as one possible embodiment) or each separately (as the embodiment PO advances)). However, the '767 Application contains no disclosure from which a

POSA would understand the inventors to be in possession of the full scope of these claimed assay agents as a whole.

It is undisputed that the '767 Application does not describe a single example of the endotoxin assay agent of challenged claim 1. POR, 31, 40. PO argues that examples are not required, but the absence of examples can support a finding of no written description. *Brita LP v. Int'l Trade Comm'n*, 156 F.4th 1326, 1332-36 (Fed. Cir. 2025) (affirming lack of written description, where the claim covered carbon-block and non-carbon block filters with a particular function, but the description had no working examples of any non-carbon-block filters—"It is not enough for the patent to simply mention a desired outcome.").

Beyond the fact that no example of the claimed assay agent as a whole is described, the vast majority of *individual elements* of that agent are *also nowhere described*. The '767 Application does not disclose:

- the sequence information for Factors C, B, or Pro-clotting enzyme for *Limulus polyphemus* horseshoe crabs;
- the sequence information for Factor B or Pro-clotting enzyme for *Carcinoscorpius rotundicuada* or *Tachypleus gigas* (neither of which were reported by 2013 (EX2062, ¶90; EX2049));

- any discussion or example of how to express Factor B or Pro-clotting enzyme in mammalian cells at all (beyond the unscientific *mutatis mutandis* boilerplate language);
- any discussion or example of the claimed endotoxin assay agent comprising the required Factors B, C, and Pro-clotting enzyme expressed from the same or different types of host cells.

PO's only response is to argue that it would have been "routine" and "predict[able]" for a POSA to fill in all of these gaps and assemble the claimed assay agents with their component parts (comprising proteins from different species, expressed in different host cells, and mixed-matched as claimed) ***and having their required "activity"***. POR, 33, 35, 40. Such gap-filling is impermissible to establish written description support where the four corners of the disclosure fail to include entire swaths of the claimed invention and PO has not established the extraneous material as well-known. *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1322-23 (Fed. Cir. 2017) (rejecting appellant's "gap-filling approach"—"The knowledge of ordinary artisans may...not [be used] to teach limitations that...would be rendered obvious by the...specification.").

1. The Coding Sequences For *Limulus Polyphemus* Factor C, Factor B, and Pro-clotting Enzyme Are Not Described And Were Not Published Until Years After 2013.

For adequate written description under §120 “[i]t is the disclosures of the applications that count.” *Lockwood*, 107 F.3d at 1571-72 (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).

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 coding sequences for *Limulus polyphemus* Factors B, C and Pro-clotting enzyme do not appear in the ’767 Application and had not been published by December 10, 2013. *See generally*, EX1017; EX1067, 32:2-24; EX1068, 258:17-20. PO has introduced evidence that bulk transcriptome data for the entire *Limulus polyphemus* horseshoe crab (approximately 188.2 million bases, EX2052, 1) had been deposited at NCBI by October 31, 2013. POR, 33-35. This information was not cited in or incorporated into the ’767 Application and its publication date was not verified. EX1067, 95:3-96:14.

Moreover, despite walking through pages of experimental protocols that a POSA “would have” followed to assemble the specific Factor C, Factor B, and Pro-clotting enzyme sequences (needle) from the horseshoe crab genome data available at the noted website (haystack), Dr. Schaefer did not actually construct the sequences. EX2062, ¶¶69-89; EX1067, 102:24-104:23; EX1068, 264:-266:10. Instead, when comparing sequences from *Limulus polyphemus* to other horseshoe crabs, Dr. Schaefer used one of the sequences provided by the inventors ***in the 2016-filed ’498 PCT to work backward.*** EX1067, 110:17-112:20; EX1068, 262:4-264:8.⁷ That is, the “blaze marks” followed by PO’s witness to understand sequence differences and make purported predictions about the protein function in the claimed assay agent 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 a host of research protocols and experiments a POSA could try (but which still lacks a disclosed sequence) is inadequate for written description of claim 1.

PO’s supplementation mirrors a similar attempt rejected in *Brita LP*, 156 F.4th at 1336. There, the Federal Circuit affirmed a finding of no written

⁷ The ’498 PCT and ’629 Publication have the same specification. EX1005, EX1015.

description where the specification did not describe the claimed non-carbon-block filters and rejected patentee's argument that because *other* non-carbon-block filter media types were known to those of ordinary skill in the art, less detail was required in the specification. *Id.* at 1336.⁸

2. The Factor B and Pro-clotting Enzyme Sequences for *Carcinoscorpius rotundicauda* and *Tachypleus gigas* Are Not Described in the '767 Application

Challenged claim 1 broadly encompasses recombinantly produced Factor B and Pro-clotting enzyme each having their respective activities not only from *Limulus polyphemus* horseshoe crabs but from *Carcinoscorpius rotundicauda* and *Tachypleus gigas* as well. However, the coding information for these proteins from these species of horseshoe crabs was unknown by 2013 and there were no available sequence deposits at all for at least *Tachypleus gigas* horseshoe crabs at that time. EX2062, ¶90. PO secured a patent (naming the three '109 Patent inventors) with a priority date of **March 1, 2017** in which those inventors admitted that the Factor B sequences from *Carcinoscorpius rotundicauda* and *Tachypleus gigas* **were not known**. EX1070, 10:11-15 (“For example, the amino acid

⁸ Petitioner's patent prosecution strategy (*see* POR, 37) is irrelevant to written description of the challenged claims. *Boston Scientific Corp. v. Cook Medical LLC*, 2023 WL 3691113, *2–*3 (S.D. Ind. 2023).

sequences of the respective polypeptides of *Carcinoscorpius rotundicauda* factor B and *Tachypleus gigas* factor B, and the base sequences encoding the polypeptides are still not known.”). There is no question that these sequences are not included, referenced, or incorporated into the ’767 Application. PO’s expert falls back on the hypothesized use of a PCR-based method to obtain these cDNA sequences (EX2062, ¶¶91-92), but PO’s expert didn’t carry out that protocol or cite to anyone who did. See EX1067, 97:10-98:1.

3. There Is No Description That The Mammalian Expression Systems for Each Zymogen Protein Be “The Same or Different”

The ’767 Application makes no mention (no literal description, experimental example, prophetic example or otherwise) of the claimed requirement that the mammalian expression systems for each recombinantly produced zymogen protein be “the same or different.” See generally, EX1017. Dr. Jain opined that the inventors’ silence here demonstrated their lack of possession of this aspect of claim 1. EX1003, ¶¶ 63-65. Neither PO nor Dr. Schaefer attempt to fill this written description hole with extraneous information.⁹

⁹ Dr. Schaefer cites EX2050 (POR, 18-19) as an extraneous description of coagulation cascade proteins from different horseshoe crab species (EX2062, ¶47),

4. PO's Extrapolations Regarding Mammalian Expression Contradict The Evidence.

Because the '767 Application does not describe most of the limitations of the claimed endotoxin assay agent, PO resorts to sweeping assertions about what a POSA would *predict* based on the limited disclosures in the '767 Application. POR, 40 ("In view of the '767 Application disclosing successful production of Factor C in two mammalian cell lines, a POSA would have understood this to be highly predictive of successful expression of Factor B and Pro-clotting enzyme in mammalian cells."). PO's cited evidence for this far-reaching assertion includes the Frohman Declaration (§§44-47), the Notice of Opposition for EP670, and Dr. Schaefer's declaration. Neither Frohman nor the Opposition involved the mammalian cell expression of Factor B or Pro-clotting enzyme (*see generally* EX2004; EX2006).

Dr. Schaefer cites Demain 2009, but that reference says nothing about horseshoe crab proteins and discusses the "drawbacks" of various systems, including mammalian cells. EX2110, 7 (drawbacks of mammalian systems include "*poor secretion*", cost, and contamination). Dr. Schaefer also cites McClymont, but McClymont is post-priority date information and McClymont actually details

but the disclosure here is of expression of proteins *in insect cells* and not in the claimed mammalian cells. EX2050, §§171, 175, 154. It does fill any gap.

failures and time constraints inhibiting her ability to use certain mammalian systems (*even as of 2017*). EX1011, 89 (“ligation of lpFC into pcR2.1 failed, with sequencing results showing empty vector or sequencing errors.”); *id.*, at 90 (“time did not allow this construct to be taken further.”).

Rather than the ease and predictability that Dr. Schaefer insists will meet POSAs trying to complete the alleged invention of claim 1, the inventors themselves described *significant challenges* with expression of Factor C in the COS-1 mammalian system, both in the ’767 Application and in the prosecution of the ’109 Patent. EX1017, ¶¶0011; EX1002, 106-111, 125-129 (“Before the priority date of the present application, it was widely known to those skilled in the art that if mammalian cells are used as a host, Factor C is not secreted.”). PO argued to the PTO that seeing Factor C secreted when expressed in CHO or HEK mammalian cells was actually “*contrary to...common knowledge*” in the field in view of prior struggles with COS-1 expression. EX1002, 126. These reports and arguments from the inventor would prevent a POSA from making sweeping assumptions about the ease of expression of newly sequenced Factor C, B, and Pro-clotting enzymes in all mammalian cell systems. EX1003, ¶¶46, 69-75, 90, 107-109.

PO also documented additional examples, prior to December 10, 2013, about struggles with recombinant expression of Pro-clotting enzyme. EX2050, ¶¶0004-5 (“Although Pro-CE has already been cloned (Non-Patent Document 2), it has been

difficult to express a protein (Pro-CE) that carries activity using this nucleic acid... Determining the base sequence of a defined protein and obtaining that protein as a recombinant and using it to construct a defined assay system are tasks that ***require highly advanced technical creativity on an entirely different level.***”). In addition, at least one reference cited in the ’767 Application itself documented attempts to recombinantly express Factor C protein with two different vectors in the same mammalian expression system, ***but success with only one.*** EX1026, 359 (“Cells transfected with pCDNAI/CrFC21 failed to generate rFC... cells transfected with pCIneo/CrFC21 indeed expressed rFC (Fig. 4).”).

Finally, even as late as 2017, Dr. Mizumura reported unpredictability in recombinant protein expression. EX1033, 143 (“Recombinant proteins, ***even with the same amino acid sequences,*** are well known to exhibit different activity and stability depending on their different post-translational modifications.”).

In view of this evidence of unpredictability, and consistent with Dr. Jain’s testimony and the evidence cited therein, a POSA would not simply extrapolate the ability to recombinantly express a functional Factor B or Pro-clotting enzyme in all mammalian cells, simply because a different protein had been expressed in HEK and CHO cells. EX1003, ¶¶72-73.

5. The Claimed Genus of Assay Agents, The '767 Application Does Not Disclose a Representative Species

Regardless of whether the claimed assay agents comprise a genus of ~3,000 or some number lower than that, the vast majority of required components of the claimed assay agents are not described in the '767 Application and were not in the possession of the inventors. As such, there is not *and cannot be* a disclosed representative species of the genus of assay agents of claim 1, no matter what its size. Such is fatal to the claim. *In re Ruschig*, 379 F.2d 990, 994 (1967) (applying written description standard to a hypothetical “class of...even 48”).

Relatedly, the written description requirement holds inventors to demonstrate possession of the full scope of their invention *as a whole*, without filling in gaps under the guise of what may have been known to a POSA, and it is clear that the inventors did not possess even a single example of such claimed assay agent as a whole. *Novozymes*, 723 F.3d at 1346-48; *Rivera*, 857 F.3d at 1322-23.

6. PO's “Functional Interchangeability” Is Not A Common Structural Feature

Recognizing that the inventors failed to disclose any representative species, PO empowers itself to use the disclosed *Tachypleus tridentatus* sequence as a proxy for all other sequences because of the “known functional similarity” across such species. POR, 46-57. But this extrapolation is not sound. If it was,

expression of *Carcinoscorpius rotundicuada* Factor C in mammalian COS-1 cells would have been successful simply because expression of *Tachypleus tridentatus* Factor C was successfully expressed in CHO DG44 cells. Instead, the inventors in the '767 Application reported (and argued strenuously in prosecuting the '109 Patent) otherwise. EX1017, ¶132; EX1002, 106-111, 125-129.

As detailed in section IV.A.4., *supra*, evidence available to POSAs as of December 10, 2013 detailed an array of challenges associated with mammalian expression of recombinant proteins such that a POSA would not interpret the gross functional similarity of native Factor C, Factor B, and Pro-clotting enzymes across species as predictive of success in expressing functional zymogen proteins from different species of horseshoe crabs in all mammalian expression systems covered by the full scope of claim 1. EX1002, ¶¶89-92. Regardless of how large 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 links the full scope of the claimed function across species proves that there is no written description as a matter of law. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598

F.3d 1336, 1350 (Fed. Cir. 2010); *Duke Univ. v. Sandoz Inc.*, 160 F.4th 1305, 1311 (Fed. Cir. 2025).¹⁰

B. A POSA Would View Completion of the Full Scope of the Claimed Invention To Require Undue Experimentation

1. A POSA Would Have to Complete A Single Example of The Claimed Assay Agent, and the Full Scope of Claim 1

“It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Regardless of the size of the claimed genus, the dispositive fact as to enablement is how little of this genus of assay agents is discussed in the ’767 Application. Instead, to reach the full scope of claim 1, the inventors left the POSA to ascertain and assemble sequences (*see* section V.A.1, 2., *supra*), design and express the resulting proteins in all mammalian expression systems (with no description of how to do so for Factors B or Pro-clotting enzyme, but with ample reports of certain mammalian systems not working, *see* section V.A.3, 4), and

¹⁰ The absence of Factors C, B, or Pro-clotting enzyme on PO’s list at POR, 57-59 suggests that the inventors’ description of the unique challenges to obtaining such information for *these* proteins bears merit. EX1005, ¶¶004-0017.

confirm the functionality of the resulting proteins as having their “activity” (in and independent from the coagulation cascade, *see* section V.A.6). EX1003, ¶¶84-122.

PO relies on the boilerplate *mutatis mutandis* language used in the ’767 Application to shortcut the inventors’ enablement obligation, but this is plainly inadequate as it **requires** the POSA to complete the required work of the inventors, particularly where the claimed Factor B and Pro-clotting enzyme had never before been expressed in mammalian cells. EX1065, 146:11-147:1, 161:4-16; *Brita LP*, 156 F.4th at 1339 (finding no enablement even though PO’s expert testified “that one could use the same ‘starting materials’ [for the claimed but unsupported embodiment] and reach the claimed invention” because that approach “essentially places the entire inventive effort on one of ordinary skill in the art.”).

As in *Brita*, PO holds itself to a suspiciously low standard and places much of the burden back on Petitioner and the POSA. POR, 61-62, 64. The vast majority of PO’s enablement citations (POR, 64-65, all those in EX2004 and EX2006) relate to the state of the art **three years later** in 2016 and relate to a different patent claim (EP670) that does not include all three of Factors C, B, and Pro-clotting enzyme. Moreover PO’s expert relies on partial knowledge and extrapolation to make the case for full-scope enablement based on the efforts of a POSA. EX2062, ¶89. However “it is not enough for enablement...that relevant

artisans knew how to perform *some*” of the claim scope. *Pac. Biosciences of Cal., Inc. v. Oxford Nanopore Techs.*, 996 F.3d 1342, 1350 (Fed. Cir. 2021).

As Dr. Jain explained, in the absence of the Factors B, C, and Pro-clotting enzyme sequences for half of the claimed species (*Limulus polyphemus* and *Tachypleus gigas*) and in view of known challenges and unpredictable results with expressing proteins in mammalian cells (*see* section V.A.4., *supra*), the experimentation required to accomplish everything in claim 1 left unexplained by the inventors as of 2013 would have been undue. EX1003, ¶¶84-122.

2. The 2019 '629 Publication Does Not Demonstrate The Inventors Enablement of Claim 1 By December 10, 2013

Having failed to establish enablement, PO relies on Petitioner’s citation to the '629 Publication as evidence that the experimentation required to make and use the full scope of claim 1 was not undue. POR, 66. But the '629 Publication is a **2019 document** offered as prior art to the challenged claims should they properly be afforded a priority date no earlier than their actual filing date. In that circumstance, the '629 Publication is enabled as an anticipatory reference *only* in so much as it discloses an enabled *example* of the claimed endotoxin assay agent. *Agilent Techs., Inc. v. Synthego Corp.*, 139 F.4th 1319, 1327-29 (Fed. Cir. 2025) (“For a *prior-art* reference to be enabling...the reference need only enable a single embodiment of the claim.”). The '629 Publication does not enable the full scope of challenged claim 1 as of 2013. *See* Section V, *supra*.

VI. CHALLENGED CLAIMS 2-9 ARE NEITHER DESCRIBED NOR ENABLED.

Claims 2-9 depend from but narrow claim 1 without reducing scope in any manner that cures the written descriptions and enablement deficiencies discussed above. PO appears to agree that these dependent claims stand or fall with claim 1. POR, 61, 75-76. For the reasons discussed in the Petition and above, claims 2-9 also lack a written description and enabling disclosures. Pet., 36-38, 55-60.

VII. CONCLUSION

Challenged claims 1-9 are unpatentable.

Respectfully submitted,

Date: 3/2/2026

/Chelsea A. Loughran/

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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 PATENT OWNER'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/
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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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