

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 OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF**

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Exhibit	Description
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: Recombinant Gene Expression: Reviews and Protocols, 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

I. INTRODUCTION

Charles River Laboratories, Inc. (“Charles River” or “Petitioner”) has petitioned for institution of challenged claims 1-9 of U.S. Patent No. 11,959,109 (“the ’109 Patent”) because those claims were erroneously granted by the Patent Office, despite the fact that they cover methods of producing an endotoxin detection assay agent comprising thousands of possible combinations of recombinantly produced horseshoe crab proteins without the specification or priority documents disclosing a *single example* of an assembly of these components for detecting endotoxin. The claims of the ’109 patent recite methods of recombinantly generating three proteins—recombinant Factor C, recombinant Factor B, and recombinant Pro-clotting enzyme (collectively known as “zymogen proteins”)—which are naturally found in the hemolymph (blood) of horseshoe crabs and which naturally undergo a clotting cascade reaction when in the presence of harmful endotoxin.

Among other arguments advanced in the Petition, the challenged claims encompass recombinantly produced endotoxin-detecting proteins from the horseshoe crab *Limulus polyphemus* despite the fact that the inventors themselves admitted in a separate patent filing that they were not in possession of such recombinant proteins when they filed their application for the ’109 Patent (a filing that has identical disclosures throughout the priority chain). The challenged claims

plainly lack adequate written description support or an enabling disclosure and were granted by the Examiner in error.

Notably, the agency has recognized this written description and enablement deficiency in a more recent filing in the same patent family. Two months ago, the *same Examiner* who allowed the challenged claims and several other patents in the continuity chain of the '109 Patent rejected very similar claims based on one of the same § 112 arguments (in the context of a priority claim rejection) advanced in the Petition. EX1042 , 2-6; Pet. 31-32. This not only demonstrates that the Examiner's earlier allowance of claims 1-9 was plain mistake, but it spotlights the merit of the Petition's arguments. Patent Owner's overreaching argument that discretionary denial should flow from the Examiner's prior consideration of § 112(a) issues during the prosecution of ancestor family member patents—including originally-filed broad claims to *all* functional Factor C—should be rejected. This is particularly true given that *same Examiner*'s more recent recognition that claims similar to those challenged in this PGR lack written description support and an enabling disclosure.

In addition, in a recent Opposition in Europe, Patent Owner has argued that the recombinant production of *Limulus polyphemus* horseshoe crab Factor C proteins was not obvious as of October 18, 2016 because “the skilled person was not motivated to produce LpFC recombinantly to improve the endotoxin detecting

agents of the prior art. There is no evidence that the skilled person would have done so in the expectation of some improvement or advantage.” EX1043 , ¶59. If recombinant *Limulus polyphemus* Factor C protein was not obvious by October 18, 2016, Patent Owner certainly did not have possession or provide an enabling disclosure of it by the December 10, 2012 claimed priority date of the ’109 Patent (or in any of the identical specifications filed in later applications in the priority chain). And in an even earlier Opposition, Patent Owner’s claims to methods of producing recombinant Factor C have been revoked “due to ... an undisclosed combination of features” found in such claims—features shared with claims 1-9. EX1044, ¶8.1.

Finally, there are significant public health considerations weighing against discretionary denial. First, the American public should not be taxed for a scope of protection that is being rejected in a recent United States case and revoked elsewhere in the world. Second, U.S. regulatory authorities have approved the use of recombinant reagents as alternatives to naturally sourced reagents from horseshoe crabs to “advance[] [their] commitment to transition methods from using animal-derived materials to synthetic and recombinant materials.” EX1051; EX1045. The subject matter of the ’109 Patent is the recombinant production of proteins otherwise found in horseshoe crab lysate (i.e., blood) that can be used in endotoxin detection assays *without* the need for harvesting such proteins directly

from animals (horseshoe crabs). Petitioner is advancing research and development on such proteins. Because claims 1-9 were erroneously granted—as demonstrated by the same Examiner’s recent rejection of similar claims—the Director should refer the Petition to the merits panel for careful evaluation of their patentability. Otherwise, these improvidently granted claims will allow Patent Owner to thwart the FDA’s efforts to transition towards synthetic and recombinant reagents for safety testing of drugs and medical devices, to the public’s detriment.

Petitioner respectfully requests that Patent Owner’s request for discretionary denial of PGR2025-0333 against claims 1-9 of the ’109 Patent be denied.

II. FACTORS FOR CONSIDERATION PURSUANT TO THE BOARD’S MEMORANDUM

On March 26, 2025, the Acting Director of the USPTO issued a memorandum regarding “Interim Processes for PTAB Workload Management” (“Memorandum”), which states that the Director will exercise discretion in institution of AIA proceedings and provides considerations for parties to address in their discretionary denial briefing. EX1046.

A. History of Prior Adjudication Against Similar Claims.

Challenged claims 1-9 are not involved in any other *inter partes* review proceedings or parallel district court litigation. However, pending claims to recombinant *Limulus polyphemus* Factor C, Factor B, and Pro-clotting enzyme in a child application to the ’109 Patent have recently been rejected for similar lack of

written description and enablement deficits (there, in the context of a rejection of the patent’s claimed priority date) as those advanced in the Petition. In addition, claims similar to challenged claims 1-9 have been pursued by Patent Owner in Europe and have been revoked (or argued patentable by Patent Owner in conflict with its arguments for patentability here) based on arguments consistent with those advanced in the Petition. These prior adjudications warrant careful consideration of the merits of Petitioner’s patentability challenge to claims 1-9.

1. U.S. Examination of App. No. 17/554,128

U.S. Patent Application No. 17/554,128 (“the ’128 Application”) is a continuation of the ’109 Patent and was filed on December 17, 2021 (claiming priority to the same Japanese priority document (JP 2012-269840), filed on December 10, 2012).

The currently pending representative independent claim (claim 3) of the ’128 Application next to challenged claim 1 is below:

Challenged Claim 1	Rejected Pending Claim 3 from ’128 Application
A method for producing an endotoxin assay agent comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising:	An endotoxin assay agent comprising a mixture of a horseshoe crab Factor C protein, a horseshoe crab Factor B protein, a horseshoe crab Pro-clotting enzyme protein, and a detection

Challenged Claim 1	Rejected Pending Claim 3 from '128 Application
	substrate for the Pro-clotting enzyme protein,
expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell, secreting the horseshoe crab Factor C into an extracellular culture supernatant, and recovering the horseshoe crab Factor C in the culture supernatant, wherein the recovered horseshoe Factor C has activity of Factor C, and wherein the horseshoe crab Factor C is a <i>Tachypleus tridentatus</i> Factor C or a <i>Limulus polyphemus</i> Factor C,	wherein the horseshoe crab is <i>Limulus polyphemus</i>, wherein the Factor C protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,
expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell,	wherein the Factor B protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,
expressing the horseshoe crab Pro-clotting enzyme having activity of Pro-clotting enzyme in a mammalian cell as a host cell,	wherein the Pro-clotting enzyme protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,

Challenged Claim 1	Rejected Pending Claim 3 from '128 Application
producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme, and wherein the host cell for expressing the horseshoe crab Factor C, the host cell for expressing the horseshoe crab Factor B, and the host cell for expressing the horseshoe crab Pro-clotting enzyme may be the same or different.	wherein the endotoxin assay agent detects an endotoxin through measuring the progress of a cascade reaction of the Factor C protein, the Factor B protein, the Pro-clotting enzyme protein, and the detection substrate,
	and wherein the endotoxin assay agent is formulated into a liquid.

EX1001, cl. 1; EX1047, 4-5.

On March 20, 2025, the Examiner (the *same* Examiner who previously examined the '109 Patent, *and* its great-grandparent '767 Application), issued a Non-Final Rejection finally denying the pending claims their asserted priority benefit. The Examiner explained—much as the Petition does—that “[t]he disclosures of the priority application nos. US 14/650,767 and

PCT/JP2013/083082¹ fail to provide adequate descriptive support and enablement in the manner provided by 35 U.S.C. 112(a) ... Claims 2, 3, 5, 15-18, and 20-23 recite *Limulus polyphemus* Factor C, Factor B, and Pro-clotting enzyme proteins that are produced through being recombinantly expressed from a HEK 293 cell. Recombinant expression of the recited *L. polyphemus* proteins from a HEK 293 cell necessarily requires cloning and expression of a polynucleotide encoding each of the *Limulus polyphemus* Factor C, Factor B, and Proclotting enzyme proteins. ***Neither the instant application nor any of the priority applications discloses a working example of cloning and expression of Limulus polyphemus Factor C, Factor B, and Pro-clotting enzyme proteins from a HEK 293 cell.*** EX1042, 3-4.

Citing Mizumura ((WO 2018/074498), relied on in Ground 3 of the Petition, where the '109 Patent inventors admitted to purportedly inventing recombinant *Limulus polyphemus* Factor C many years ***after*** the priority date of challenged claims 1-9) and McClymont (the 2017 disclosure of the gene and amino acid sequences for *Limulus polyphemus* Factor C), the Examiner of the '128 Application concluded: "In view of the noted disclosures of McClymont and

¹The disclosures of US 14/650,767 and PCT/JP2013/083082 are materially identical to the specifications of later applications in the priority chain of the '109 Patent in that patent specification itself. Pet. 23-24, n. 6.

Mizumura, one of skill in the art would have recognized that the *disclosures of priority application nos. U.S. 14/650,767 and PCT/JP2013/083082, which were filed prior to the publications of McClymont and Mizumura, fail to adequately describe and enable cloning and expression of a polynucleotide encoding each of the L. polyphemus Factor C, Factor B, and Pro-clotting enzyme proteins from a HEK 293 cell.*” EX1042, 6.

As discussed in Section III, *infra*, regarding material error, the Examiner of the '109 Patent (and its ancestors back to the '767 Application) never recognized this deficiency in the priority disclosure and subsequent identical applications and failed to reject pending claims accordingly. Now, nearly a decade later, the same Examiner has recognized this flaw, articulated this defect in prosecution of claims to recombinant Factor B, Factor C, and Pro-clotting enzyme from *Limulus polyphemus* horseshoe crabs, and has **rejected** those claims. EX1042, 2-11.

It is incumbent on this Board to carefully examine challenged claims 1-9 in the same light to avoid inconsistent results impacting the public in this important area of public health. The Board should refrain from exercising its discretion and foregoing this important opportunity to rectify an error the Patent Office is actively addressing in other proceedings in the same family.

2. Opposition Against European Patent EP 3 530 670

On November 22, 2024, a Notice of Opposition was filed against Patent Owner's EP 3 530 670 ("EP670"), which claims priority to Japanese priority document (2016-204729, filed October 18, 2016)) ("EP670 Opposition"). EP670 is unrelated to the patent family that includes the '109 Patent and contains a different specification. The EP670 Opposition seeks revocation of Claim 1:

A method for producing an endotoxin detecting agent, comprising
a step of artificially expressing a protein using a cDNA, and collecting
the expressed recombinant protein as a solution fraction containing
the expressed recombinant protein,

wherein the cDNA encodes any one of the following:

(A) a recombinant protein expressed as containing the amino acid
sequence represented by SEQ ID NO: 2 or 4;

(B) a recombinant protein expressed as containing an amino acid
sequence having a 95% or more identity with the amino acid sequence
represented by SEQ ID NO: 2 or 4, and has factor C activity; and

(C) a recombinant protein that is encoded by a DNA containing a base
sequence having a 95% or more identity with the base sequence
represented by SEQ ID NO: 1 or 3, and has factor C activity, and

wherein the solution fraction containing the expressed recombinant
protein is a culture solution, or a culture supernatant.

EX1048, ¶8.

SEQ ID Nos: 1-4 are the base and amino acid sequences of *Limulus polyphemus* horseshoe crabs. EX1005, ¶0022. As Patent Owner notes in its Brief (Paper 6, “Br.” at 33), the Opponent in this case argued that as of the October 18, 2016 priority date of the opposed claims “[i]t would have been obvious to use the claimed method to recombinantly produce [recombinant *Limulus polyphemus* Factor C] for the following reasons.” EX1048, ¶¶28-29. Patent Owner argues that such argument somehow contradicts the Petition and that the contradiction supports discretionary denial. Br. 21-23, 31-35.

But no contradiction exists. First, EP670 and the ’109 Patent are in different patent families, have different priority dates, and have different specifications.

Second, despite Patent Owner’s assertion, there is nothing inconsistent about the argument, on the one hand, that as of October 18, 2016, it would have been obvious to a POSA to determine the amino acid sequence of *Limulus polyphemus* horseshoe crab Factor C and attempt the recombinant production of the same, and the separate argument, on the other hand, that the inventors of the ’109 Patent did not possess, sufficiently to describe, or enable the breadth of challenged claims 1-9 (including the recombinant expression of *Limulus polyphemus* zymogen proteins, as they themselves admitted) in their priority filings or identical specifications filed thereafter. *Rivera v. Int’l Trade Comm’n*, 857 F.3d 1315, 1322-23 (Fed. Cir. 2017) (affirming a finding of no Tariff Act violation based on finding that even if an

embodiment within the scope of the asserted claim was obvious to one of skill based on the specification, that did not show that the inventor possessed that scope); *Lucent Techs., Inc. v. Gateway, Inc.*, 543 F.3d 710, 719 (Fed. Cir. 2008) (rejecting priority claim—“The district court determined that the ’457 patent (which shares the same specification as the ’598 application filed in 1988) does not mention MDCTs and thus there is no evidence that the work embodied in claim 2 was performed prior to April 1989. Even if the implementation of MDCTs into the claimed technology would have been obvious to one of skill in the art, the court correctly recognized that a demonstration of obviousness is not sufficient to show possession.”). Patent Owner makes this very point in its Reply to the EP670 Opposition. EX1043, ¶53 (“[T]he applicable standard at the USPTO for determining whether an Applicant is in possession of the full scope of the claims *is not the same as* required by the EPO’s could-would approach.”).

Finally, *it is Patent Owner* who has undermined its priority claim by arguing in Europe that the leap from generating recombinant Factor C from the *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* species of horseshoe crab to *Limulus polyphemus* would not have been obvious as of October 18, 2016. EX1043, ¶59. If such advance was not obvious as late as 2016, the ’109 Patent inventors certainly did not describe it in sufficient detail to be in possession of such an advance when they first filed the application giving rise to the ’109 Patent in 2012 (provisional),

or 2013 (PCT), or in any of the identical specifications filed in the priority chain since then. It is well settled that the obviousness of trying a particular course in view of the prior art is insufficient to constitute an adequate written description of a claim to that course. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997) (no written description—for entitlement to priority benefit under 35 U.S.C. § 120, “each application in the chain leading back to the earlier application must comply with ... § 112. ... [and] [i]t is the disclosures of the applications that count. Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed.”); *see also In re Kuenzel*, Appeal 2009-015373, 2011 WL 938717, at *5 (B.P.A.I. Mar. 17, 2011) (finding claimed subject matter not entitled to earliest alleged priority date—“One shows that one is ‘in possession’ of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.”); *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (“A description that merely renders the invention obvious does not satisfy the requirement.”).

Patent Owner’s assertions in the EP670 Opposition confirm Petitioner’s uncovering of a lack of written description and enablement disclosure for the ’109 Patent and the unpatentability of challenged claims 1-9 as a result. Discretionary denial should be reserved while this Board can consider the merits of the Petition.

3. Opposition Against European Patent EP 3 441 466

On November 5, 2020, a Notice of Opposition was filed against Patent Owner's EP 3 441 466 ("EP466"), which claims priority to the same Japanese priority document as the '109 Patent and shares the same specification. ("EP466 Opposition").

While the specific claims at issue in EP466 were amended over the course of that Opposition, the representative claim 1 of the Main Request considered for resolution by the Opposition Decision recited the following (bolded text overlaps with challenged claims 1-9):

A method for producing a water soluble horseshoe crab Factor C for use in endotoxin assay in the presence of a salt ion, the method comprising:

expressing the horseshoe crab Factor C in a human embryo kidney cell or a Chinese hamster ovary cell as a host cell, wherein the thus-expressed horseshoe crab Factor C is detected in a soluble fraction, **and recovering the expressed horseshoe crab Factor C as a solution containing the horseshoe crab Factor C, which is a culture supernatant containing Factor C,**

wherein the Factor C has activity of Factor C,² and contains (α-2,3)-linked terminal sialic acid in a greater amount, as compared with a horseshoe crab Factor C expressed using Sf9 as a host cell, and wherein the Factor C exhibits higher residual activity in the presence of 52 mM sodium hydrogencarbonate, as compared with a horseshoe crab Factor C expressed in Sf9 as a host cell,

and wherein the activity of Factor C is an activity that the Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B.

EX1044, ¶6.1.

This claim was revoked “due to the presence of combinations of individualised features selected from multiple lists ... and the presence of ... an undisclosed combination of features.” EX1044, ¶8.1. While European legal standards including the requirements of Articles 76(1) EPC and 123(2) EPC differ from United States patent law and the standards applied by United States Examiners and this Board regarding patentability, the finding of a failure of the

² Both the revoked EP466 claims and claims 1-9 recite “Factor C [having] activity of Factor C.” The ’109 Patent defines “activity of Factor C” as “confirmed, for example, by combining the Factor C of the present invention with a suitable Factor B and a suitable Pro-clotting enzyme in the presence of endotoxin, and detecting the progress of the cascade reaction.” EX1001, 15:66-16:4.

common specification to disclose features shared by the opposed claims in Europe and challenged claims 1-9 in this proceeding weighs in favor of a close examination of those claims now.

B. There Is No Inconsistency Between The Grounds Advanced In The Petition And Arguments Made In Other Proceedings.

Patent Owner argues that the Director should exercise her discretion because arguments and expert testimony submitted in support of the EP670 Opposition “are directly contradictory to its arguments in the Petition. And statements made in Petitioner’s own patents are inconsistent with its positions here.” Br. 21-22.

1. There Is No Inconsistency Between The EP670 Opposition Arguments And Those In The Petition.

As discussed in Section II.A.2., *supra*, the obviousness-type arguments made in the EP670 Opposition³ do not contradict the written description and

³ While entirely immaterial to the Director’s review, PO suggests that because certain of the prior art references submitted with the Petition bear watermarks similar to those filed in connection with the EP670 Opposition, the Opponent and Petitioner must have the same identity. The prior art references cited in support of the Petition that were also cited in support of the EP670 Opposition (certain of which also overlap with those cited in the EP466 Opposition) were filed publicly in connection with those Oppositions and were available online from the European

enablement arguments advanced in the Petition.⁴ Dr. Frohman provided testimony explaining why, **by October 18, 2016**, it would have been obvious (under European patent standards, and in view of the guidance provided in the specification of EP670) for a POSA to use the EP670 claimed method to recombinantly express *Limulus polyphemus* horseshoe crab Factor C.⁵ By contrast, Dr. Frohman provided

Patent Register before the Petition was filed. Any member of the public noting the sound arguments of Opponent and stiff skepticism of the EPO regarding Patent Owner's claims to recombinant *Limulus polyphemus* Factor C, could have accessed those references (bearing the watermarks as noted) and used them to compile a post-grant review of claims 1-9 of the '109 Patent.

⁴ Even were such arguments found to be contradictory or concessionary in any way, there is no basis for this Board to bind Petitioner to the anonymously-filed Opposition statements. *Xerox Corp. v. Monument Peak Ventures, LLC*, IPR 2022-00318, Paper 7 at 17, n.7 (PTAB June 9, 2022) (granting institution where Board refused to rely on an argument made by Petitioner based on an “express[] conce[ssion]” made before the EPO because “Petitioner identifies no legal basis for binding Patent Owner to that alleged concession in this proceeding.”).

⁵ The U.S. counterpart to EP670 (U.S. App. No. 16/331,810) faced a number of obviousness rejections during prosecution including obviousness over the earlier

no opinion, evidence, or other testimony relating to whether Applicant possessed or enabled the recombinant proteins of claims 1-9 based on the disclosures provided in the specification of a *different patent* (the '109 Patent priority disclosure and identical subsequently filed specification, which is in a different patent family from EP670), nearly four years earlier. Contrary to Patent Owner's bald assertion, Opponent did not argue that—and Dr Frohman made no statements and offered no opinions regarding whether—the '767 Application adequately describes or enables challenged claims 1-9. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1310 (Fed. Cir. 2008) (ruling that expert's statement that it would have been obvious to make a modification did not suffice to show adequate written description support—"At best, this is [an expert] statement that it would be obvious to substitute a customer laptop for the user interface disclosed on the vending machine. Obviousness simply is not enough; the subject matter must be disclosed to establish possession.").

Patent Owner states, "[t]he only evidence cited in the Petition in support of the foundational premise that there would have been any difficulty in sequencing and expressing *L. polyphemus* Factor C, are statements made in the '629

publication of the '109 Patent's great-grandparent application (App. No. 14/650,767). Patent Owner abandoned that application. EX1050.

Publication.” Br. 31. Not only is this an incorrect reduction of the written description and enablement requirements—neither test boils down to whether it would have been “difficult” to carry out the full scope of the claimed invention—it is simply untrue as a factual matter. First, the ’629 Publication contains the ’109 Patent inventors own admissions about what they knew and, presumably, believed to be true. Second, Petitioner’s expert, Dr. Siddhartha Jain, testified via expert declaration regarding the ways in which protein function is defined by its structure such that even small differences in protein sequence (as would be expected for different species of a given animal) can lead to differences in structure, and thus function. EX1003 (“Jain”), ¶72.

Dr. Jain also explained that while recombinant technology was not new as of 2013, a significant amount of research and experimentation was still required to generate a particular protein, in a functional state. *Id.* ¶89. Thus, even if Professor Frohman opined in connection with the EP670 Opposition that obtaining the cDNA sequence for *Limulus polyphemus* Factor C would not have been difficult as of October 18, 2016, such opinion does not contradict the distinct legal and factual arguments advanced in the Petition that, for several reasons, the inventors did not describe a single example of or enable the full scope of challenged claims 1-9 (which is a method of producing an endotoxin assay agent encompassing over

three thousand combinations of recombinantly expressed zymogen proteins—including, but not limited to, *Limulus polyphemus* Factor C).

2. There Is No Inconsistency Between Petitioner’s Own Statements In Its Patent Filings and the Petition.

With respect to Patent Owner’s citation of statements made in U.S. Patent No. 6,391,570 (“the ’570 Patent” (EX1061), 1:47-48), Petitioner does not dispute that the endotoxin detection mechanism of natural amebocyte lysate for *Limulus polyphemus* had been known and characterized well prior to 2012. The LAL assay dates back to the 1980s. The ’570 Patent, however, has nothing to do with recombinant expression of zymogen proteins—it relates only to “improved amebocyte lysate preparations [i.e., naturally sourced proteins] having reduced Factor G activity.” EX1061, 2:61-65. Moreover, the fact that the ’570 Patent states that the endotoxin-detecting abilities of natural lysate were known has no bearing on whether the ’109 Patent inventors described and enabled a method of producing an endotoxin assay encompassing over three thousand combinations of recombinantly expressed zymogen proteins—including recombinant *Limulus polyphemus* Factor C.

Likewise, U.S. Patent No. 10,473,663 (“the ’663 Patent”) is directed to “LAL” or the *Limulus* amebocyte lysate. While the specification mentions that this “could include” recombinantly produced components, the patent does not discuss or relate to recombinant zymogen production at all. The ’663 Patent has no

bearing on the written description or enablement inquiries raised in the Petition against the '109 Patent. Patent Owner's arguments regarding these statements in Petitioner's patents are irrelevant to the Director's exercise of her discretion.

C. The Board's Exercise of its Discretion Would Hinder Regulatory Efforts to Transition From Animal-Derived to Synthetic or Recombinant Reagents For Detecting Endotoxin.

The Memorandum permits the parties to address "compelling economic, public health, or national security interests" that may be relevant to the question of discretionary denial of the petition under consideration. Memorandum, 2. Failure to carefully consider and weigh the merits of the Petition in this case would run counter to compelling public health and regulatory interests.

The technology at issue with respect to the '109 Patent is a recombinant protein substitute for a protein sourced from horseshoe crabs and used in LAL tests (or, "limulus tests"). The LAL test (*Limulus* Amebocyte Lysate) is a widely used method for detecting and quantifying bacterial endotoxins in various biological products and materials. Endotoxins, a type of pyrogen (fever-inducing substance), can be harmful if present in products that come into contact with the bloodstream. EX1001, 1:36-2:12. Horseshoe crab lysate (the equivalent of horseshoe crab "blood," from which the endotoxin-detecting Factor C protein is sourced) used in traditional LAL tests comes directly from the horseshoe crabs themselves via a non-lethal harvesting procedure. EX1005, ¶¶0002-08. Challenged claims 1-9 are

directed to methods or producing an alternate endotoxin detection assay by *recombinantly* producing Factor B, Factor C, and Pro-clotting enzyme proteins where this assay has the endotoxin detecting ability of native LAL but is generated in a laboratory without the need to harvest lysate directly from horseshoe crabs. EX1001, cls. 1-9.

In conjunction with the Food and Drug Administration, the U.S. Pharmacopeia (an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines) has recently *approved* the use of “recombinant reagents as alternatives to naturally sourced reagents from horseshoe crabs (LAL or TAL)” for the “purposes of quantitating endotoxins activity in injectable drugs, biologics and medical devices.” EX1051; EX1045. This approval has been granted explicitly to “advance[] USP’s commitment to transition methods from using animal-derived materials to synthetic and recombinant materials.” *Id.*

Petitioner has invested over \$6 million, with additional spend anticipated, to develop a synthetic, recombinantly produced alternative to LAL, such as recombinant Factor C. Petitioner’s investment directly advances US Pharmacopeia’s commitment to transition to such synthetic alternatives. The public has an interest in the advancement of this transition (and Petitioner’s investment in the same) both to expand alternatives for endotoxin testing of critical

drugs and other medical devices but also to enable competition (and facilitate accompanying price controls).

If allowed to stand, challenged claims 1-9, which issued on April 16, 2024 (based on an earliest claimed priority date of December 10, 2012) will prevent would-be competitors from developing endotoxin detection assays incorporating recombinant *Limulus polyphemus* Factor C proteins for another two decades. It will hinder the regulatory and public health transition from “using animal-derived materials to synthetic and recombinant materials.” EX1051; EX1045.

Accordingly, the public has a strong interest in the Board’s careful review of the merits of patentability of challenged claims 1-9.

D. The Strength of the Unpatentability Challenge, Properly Lodged As A Post-Grant Review, Weighs Against Discretionary Denial.

Petitioner’s challenge to claims 1-9—properly framed as a post-grant review—further counsels against discretionary denial. Patent Owner argues that discretionary denial should flow from the fact that Petitioner’s challenge is not properly framed as a Post-Grant Review (Br., 10-21). Patent Owner’s arguments should be rejected for several reasons.

First, Patent Owner incredibly argues that the ’109 Patent is not PGR eligible after insisting the exact opposite in writing to the agency in prosecution. (EX1022). Patent Owner now claims its deliberate, stand-alone Transition Application Notice—serving no other purpose but to identify AIA eligibility—

should somehow be ignored. As discussed more fully below, the transition statement is determinative and demonstrates PGR eligibility.

Even were the transition statement somehow not determinative, however, the JP Priority Document to which the '109 Patent claims priority does not support or enable the full scope of challenged claims 1-9. Challenged claim 1 recites a method of producing an assay agent where the components of that assay have a particular *activity*. Neither Patent Owner's Japanese priority document, nor its later PCT filing, nor any other application in its priority chain including the specification as filed, sufficiently describes recombinantly expressed Factor C, Factor B, or Pro-clotting enzyme proteins (or the thousands of claimed combinations thereof) having the particular *activity as claimed* such that a POSA would have understood those inventors to have described and enabled the full scope of the methods of challenged claims 1-9. The challenged claims are eligible for post-grant review.

1. Patent Owner's Transition Statement Secured AIA Treatment for The Challenged Claims During Examination and Requires That Those Claims Are Eligible for PGR Now.

Patent Owner filed a "Statement Under 37 C.F.R. § 1.55 or § 1.78 for AIA (First Inventor to File) Transition Applications" (the "transition statement") during the prosecution of Application No. 15/983,725 (the "'725 Application"), a great grand-parent application to the '109 Patent. EX1022. As a result, each subsequent

application claiming priority to the '725 Application was evaluated by the Patent Office under the provisions of the AIA. *See, e.g.*, EX1056, 2 (“The present application ... is being examined under the first inventor to file provisions of the AIA”). Patent Owner now argues that the transition statement is not determinative of whether the certain provisions of the AIA apply to the '109 patent. Br., 10-11. Patent Owner’s assertion should be rejected for at least two reasons.

First, Patent Owner states that “Petitioner makes no showing that this transition statement ... applies to any specific feature of the Challenged Claims.” *Id.* at 11. Patent Owner filed EX1022 during prosecution of the '725 Application, from which the '109 Patent claims priority. A transition statement is not required for later applications “if the application claims the benefit of a nonprovisional application in which such a statement ... has been filed.” MPEP § 210.III(A); *see also* Pub. L. 112-29, § 3(n), 125 Stat. 284 (2011) (“the amendments made by this section ... shall apply to any application for patent, and to any patent issuing thereon, that contains or contained at any time—(A) a claim to a claimed invention that has an effective filing date ... that is on or after the effective date described in this paragraph; or (B) a specific reference under section 120, 121, or 365(c) ... to any patent or application that contains or contained at any time such a claim.”). In addition, a transition statement need not “indicate which particular claim or claims have a post March 16, 2013 effective filing date,” since this information is not

necessary to determine whether the AIA applies. 78 Fed. Reg. 11040-41. As a result, the transition statement applies for all claims in all applications that claim priority to the '725 Application, including all claims of the '109 Patent. The transition statement was correctly submitted at least because the claims pending when it was filed in that ancestor application (the '725 Application) encompass recombinant Factor C protein from *Limulus polyphemus* horseshoe crabs which, as the Petition explains, the inventors neither described nor enabled in either their pre-AIA priority filing nor their later more fulsome PCT filing. Pet. 9-11, 23-60.

Second, Patent Owner asserts that transition statements are “revocable” and “must be weighed ‘against the other evidence’ submitted in a proceeding.” Br., 11. Patent Owner has not revoked this transition statement. And the MPEP does not state that transition statements are “revocable,” as Patent Owner implies, rather it provides that “the Office *may require* the applicant to identify where there is written description support ... in the pre-AIA application for each claim to a claimed invention *if the applicant ... later argues that the application should have been examined as a pre-AIA application.*” MPEP § 210.III(A) (emphasis added). Patent Owner does not argue that the claims of the '109 Patent should have been examined as pre-AIA applications. To the contrary, Patent Owner gained certain benefits of AIA examination that it presumably does not now want to forfeit. There is no evidence that Patent Owner believed the '109 Patent

application should have been examined as a pre-AIA application, despite having many opportunities to do so, for example, in response to the September 15, 2023 Non-Final Rejection, which again stated: “The present application...is being examined under the first inventor to file provisions of the AIA.” EX1056, 2.

The two cases that Patent Owner cites for the proposition that its own attestation that its claims should have been examined under the AIA but should now not be subject to post-grant review are inapposite. Neither case involves PTAB procedure, let alone the complex circumstances involved with transition applications. Nor do the cases support Patent Owner’s argument that its transition statement is not determinative of the ’109 Patent’s AIA status.

In *Paice*, Toyota sought to treat a statement regarding a non-infringing design made by Paice’s counsel as a binding judicial admission, but the district court held that the statement was merely an evidential admission, not a conclusive admission, and that “the jury was free to weigh [it] against the other evidence adduced at trial.” *Paice LLC v. Toyota Motor Co.*, 504 F.3d 1293, 1312 (Fed. Cir. 2007). The Federal Circuit agreed with the district court “in light of ... the ‘conclusory’ nature of the admission itself.” *Id.* Unlike the statement in *Paice*, Patent Owner’s transition statement was not “conclusory” and binds Patent Owner to post-AIA evaluation.

In *Shell*, the Government sought to exclude the parties' stipulation and statements from an earlier litigation. *Shell Oil Co. v. United States*, 896 F.3d 1299, 1312 (Fed. Cir. 2018). The Federal Circuit in that case held that the Court of Federal Claims did not abuse its discretion by considering the statements and stipulation, and that "based on all evidence on record, the Stipulation and Parties' Statements supported its findings on damages with reasonable certainty." *Id.* Beyond simply supporting a finding that the AIA applies for the '109 Patent, the transition statement is an explicit acknowledgement (and admission) by Patent Owner (the entity in the best position to know) that the AIA applies.

Patent Owner's transition statement and resulting AIA examination of the challenged claims require that those claims are also subject to post-grant review as set forth in the AIA.

- 2. Challenged Claims 1-9 Are Neither Described Nor Enabled By The Japanese Priority Document.**
 - a. Challenged Claims 1-9 Require Three Functional Zymogen Proteins That Each Drive Their Portion of the Endotoxin Detection Cascade Reaction.**

Regardless of the impact of the transition statement, the JP Priority document for the '109 Patent neither describes nor enables the challenged claims. This is an independent reason for post-grant eligibility. Patent Owner's arguments to the contrary (Br., 11-20) should be rejected.

Claim 1 of the '109 Patent recites a “method for producing an endotoxin assay agent” comprising the performance of several steps, including the generation of recombinant proteins, which are able to be secreted and recovered, ***and which have a particular function.*** For example, claim 1 requires (1) the expression of horseshoe crab Factor C via certain expression systems and from certain horseshoe crab species, (2) the secretion and recovery of this protein, and (3) that this protein have “activity of Factor C.”

In addition, the '109 Patent repeatedly instructs that the “endotoxin assay agent of the present invention” can be different ***depending on the function desired.*** EX1001, 20:7-19 (“The endotoxin assay agent of the present invention may further contain a factor or factors other than Factor C, ***depending on the mode of endotoxin assay.*** For example, the Factor C of the present invention may be used in combination with Factor B and Pro-clotting enzyme, ***for endotoxin assay.***”).

The '109 Patent describes that the claimed “endotoxin assay agent” can be different depending on whether it is desired to detect enzyme by detecting Clotting enzyme as the final product of the cascade reaction of the three zymogen proteins, or merely detect an intermediate stage of such reaction. *Id.* 20:19-39. Moreover, claim 1 requires that all three of the zymogen proteins have “activity of” those proteins, meaning that the claimed “method of producing an endotoxin assay agent” requires that the components generated exhibit a function to enable the

“assay” to perform its purpose of detecting endotoxin. EX1001, cl. 1. The ’109 Patent defines “**activity of**” each zymogen protein as the functional activation and triggering of the next step in the cascade reaction:

The **activity of Factor C** refers to such an activity that the **Factor C is activated in the presence of endotoxin to convert Factor B into activated Factor B**. Whether “the Factor C of the present invention has activity of Factor C” can be confirmed, for example, by combining the Factor C of the present invention with a suitable Factor B and a suitable Pro-clotting enzyme in the presence of endotoxin, and detecting the progress of the cascade reaction.

EX1001, 15:64-16:9.

The **activity of Factor B** refers to such an activity that the **Factor B is activated in the presence of activated Factor C to convert Pro-clotting enzyme into the activated form thereof**, i.e. the corresponding Clotting enzyme. Whether “the Factor B of the present invention has activity of Factor B” can be confirmed, for example, by combining the Factor B of the present invention with a suitable Factor C and a suitable Pro-clotting enzyme in the presence of endotoxin, and detecting the progress of the cascade reaction.

EX1001, 21:3-16.

The *activity of Pro-clotting enzyme*⁶ is such an activity that the *Pro-clotting enzyme is converted into the activated form thereof, i.e. the corresponding Clotting enzyme, in the presence of activated Factor B, to react with the below mentioned substrate for detection*. The activity of reacting with the detection substrate refers to, for example, an activity of reacting with a coagulogen to induce coagulation ... Whether “the Pro-clotting enzyme of the present invention has the activity of Pro-clotting enzyme” can be confirmed, for example, by combining the Pro-clotting enzyme of the present invention with a suitable Factor C and a suitable Factor B in the presence of endotoxin, and detecting the progress of the cascade reaction.

EX1001, 21:31-53.

Patent Owner concedes that claim 1 requires “the expression of *functional* Factor C ... *functional* Factor B and Pro-clotting enzyme.” Br., 13.

To suggest that claim 1 does not require a functional confirmation or verification that the recombinantly produced zymogen proteins have the *claimed activity* to be activated and to activate the next component of the cascade reaction

⁶ Claim 1 initially issued without this language regarding “activity of Pro-clotting enzyme” but Patent Owner filed a certificate of correction on April 16, 2024 to add this functional requirement back in. EX1001, Certificate of Correction, 1 (“Claim 1, Line 32, please delete ‘Pro-clotting enzyme in a’ and insert --Pro-clotting enzyme having activity of Pro-clotting enzyme in a-- therefor.”).

flies in the face of the exact words and phrases *that Patent Owner itself chose* and defined in its patent. Even if claim 1 does not explicitly require the ultimate performance of measuring endotoxin detection, the functional requirements of the components required by the claimed method of producing an endotoxin assay dictate that for the inventors to have described and enabled the claimed method, they had to demonstrate the ability to generate an assay agent with the *functional components* claimed. *University Of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (no written description—"[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.""). The Petition aptly demonstrates that neither the JP Priority document, nor any application in the priority chain of claims 1-9 provided a written description or an enabling disclosure of a single assay comprising a combination of functional zymogen proteins as claimed. Pet., 9-11, 23-60.

Moreover, Patent Owner's disclaimer of claim 10 effectively concedes that it did not support or enable a claim to a functional endotoxin detection system that "measures the progress of a cascade reaction." However, given the fact that both disclaimed claim 10 and challenged claim 1 require each zymogen protein to "hav[e] the activity of" that zymogen protein—which are the components driving

the cascade reaction itself—the scope of these claims is not materially different and the lack of support and enablement detailed in the Petition applies to both.

b. The '840 JP Priority Document Does Not Describe or Enable the Functional Components of Challenged Claims 1-9.

As detailed in the Petition, the '840 JP Priority Document provides no disclosure or guidance regarding how a POSA would make or use the functional assay agent of exemplary challenged claim 1 with Factor B or Pro-clotting enzyme recombinantly produced in a mammalian expression system. Pet. 10-11. The '840 JP Priority Application does not discuss or teach the recombinant production of Factor B or Pro-clotting enzyme via any system other than Sf9 insect cells. EX1008, ¶¶0112-14. Nor does the '840 JP Priority Application disclose or teach how to generate the claimed assay agent via three functional recombinantly produced zymogen proteins expressed via *different* mammalian cell lines or with sequence information from *different* species of horseshoe crabs as claimed. *See generally*, EX1008; Pet. 10-11.

Patent Owner points to general and sweeping statements in the '840 JP Priority Document where the inventors claimed that while they only were able to produce Factor B and Pro-clotting enzyme proteins in insect cells, a POSA could just apply the same teaching to mammalian expression systems. Br., 18 (citing EX1008 at 13 (¶ 0052) (“[w]hen animal cells such as mammalian cells are used,

the above-mentioned description of the production of factor C of the present invention can be applied correspondingly to the production of factor B and pro-clotting enzyme.”)). But in an unpredictable area such as the recombinant production of proteins, it is not enough to merely claim the same technique used in one expression system could be used in an entirely different system (insect versus mammalian). As the Petition points out, even the inventors noted (in the ’840 JP Priority Document itself) that prior attempts to recombinantly produce *functional* Factor C protein *in mammalian systems* had failed.

Alternatively, there is known a case of using mammalian cells as host cells, wherein Factor C derived from the Singaporean horseshoe crab (*Carcinoscorpius rotundicauda*) was expressed in COS-1, which is a cell line derived from African green monkey kidney cells, as host cells. However, it has been reported that when COS-1 was used as a host, the expressed Factor C was insoluble (Non-Patent Documents 3 and 4). That is, there has never been known a case where functional Factor C is produced using mammalian cells as host cells.

EX1001, 44:53; *see also* Pet., 42-43.

And while the above skepticism relates to Factor C produced in mammalian cells, the ’840 JP Priority Document is *entirely silent* on the mammalian expression of Factor B and Pro-clotting enzyme, two completely different proteins whose production in mammalian cell lines is not even mentioned, let alone described and enabled by the ’840 JP Priority Document.

Patent Owner's noting that the '840 JP Priority Document explains how the inventors produced Factor C in mammalian cells (Br., 18) likewise does not demonstrate that the inventors described or enabled the recombinant production of the distinct zymogen proteins (Factor B and Pro-clotting enzyme) in a mammalian expression system. Patent Owner claims that the Petition provides no evidence that the techniques in these examples for expressing Factor C could not be "applied correspondingly" to expressing Factor B and Pro-clotting enzyme. (Br. 18). But Patent Owner ignores Dr. Jain's testimony in which he explains that "having known in the field that the expression of a functional protein is dependent on the specific protein and expression conditions (and purification conditions, as applicable such as when extracted by cell lysis), a POSA would not have assumed they could obtain a functional recombinant Factor B and Pro-clotting Enzyme by replicating the expression process for recombinant Factor C." Jain, ¶61; *see also id.* at ¶71 (explaining the difficulty and unpredictability of recombinant protein expression as of 2013). Patent Owner's unsupported assertion that the inventors described and enabled the recombinant expression of Factor B and Pro-clotting enzyme (both "having the activity of" each protein) in a mammalian expression system by simply disclosing (1) the recombinant expression of these proteins in insect cells, and (2) the recombinant expression of *different* proteins in mammalian cells, is flatly contradicted by the evidence of record.

Similarly, Patent Owner’s assertion that the general identification of the “four species of horseshoe crab as ‘examples of horseshoe crabs’” constitutes a written description or enabling disclosure of the ability to recombinantly express the three zymogen proteins in mammalian cells across the full scope of claim 1—including in the *Limulus polyphemus* horseshoe crab—is belied by the overwhelming evidence presented in the Petition to the contrary. Most notably, as discussed above and in the Petition, the inventors themselves admitted to **not** being in possession of the gene or amino acid sequence for this species of horseshoe crab until 2017 despite such sequences being known for other species (a fact the Examiner in Patent Owner’s current pending cases now recognizes in denying the asserted priority claim of related, pending claims). EX1042, 6; EX1015 (“the ’629 Publication”), ¶¶0007-12 (“[I]n *Limulus polyphemus*, complete identification of these proteins and genes from both structural and functional aspects has not been achieved even though 20 years or more has passed since the reports regarding the genus *Tachypleus* described above were published. This is because accurate determination of the full-length sequence structures and elucidation of the expression and functions of these proteins and genes could not be achieved by general techniques due to various differences in biomolecules, diversities, etc. because of differences in genera or species of horseshoe crabs.”); EX1005, ¶¶0010-

12; *see also* EX1038, 6-7, 10-15 (discussing discreteness of Family *Limulidae* and Family *Tachypleinae*); Jain, ¶67.

Finally, as explained in the Petition, the scope of claim 1 covers at least 3,456 possible combinations of zymogen proteins to arrive at the claimed “method for producing an endotoxin agent.” Pet. 27-28. Patent Owner points to the ’840 JP Priority Document’s “examples of preparing endotoxin assay agents where factor C proteins from different sources, including mammalian cells, are combined with recombinant factor B and Pro-clotting enzyme from Sf9 cells.” Br., 19. But not one of these “examples” fall within the scope of the claims (which require Factor B and Pro-clotting enzyme to be expressed in *mammalian cells*). These examples do not constitute disclosure of even a single representative species of the vast genus defined by challenged claim 1.

The ’840 JP Priority Document, filed on December 10, 2012, does not disclose a single example falling within the thousands of combinations of recombinantly produced functional zymogen proteins defined by claim 1, filed *over a decade later*. And none of the limitations appearing in dependent claims 2-9 serve to limit claim 1 in any manner that would remedy this inadequate written description support and enablement. Pet. 36-38, 55-60. Challenged claims 1-9 are not entitled to the priority filing of the ’840 JP Priority Document which (along

with Patent Owner's own transition statement attesting to the same) renders those claims eligible for post-grant review.

3. This Properly Lodged PGR Is Well-Suited For Consideration on the Merits.

There is a fatal flaw running through Patent Owner's patent estate and Patent Owner is repeatedly gaining the benefit of patent monopoly rights despite not having invented the breadth it claims as of the December 10, 2012 claimed priority date of its patents. The Patent Office has finally noticed this flaw and is issuing rejections in active cases accordingly, but post-grant review is the perfect vehicle to remedy the Examiner's prior error in issuing claims 1-9 of the '109 Patent. As the Director has noted, "post-grant reviews filed soon after a patent is issued 'can also help improve the durability of patent rights' ... [particularly where] companies scour issued patents for those that could impact their business." EX1057, 2. The instant case is precisely the scenario that the Director is referencing. Petitioner has uncovered this flaw in Patent Owner's claims—claims that directly impact Petitioner's business (as well as the public health, *see* Section II.C. *supra*)—and is promptly using post-grant review as an immediate and efficient means for bringing this flaw to the Patent Office's attention and seeking reconsideration of these improvidently granted claims. Patent Owner's request for discretionary denial should be denied.

III. DISCRETIONARY DENIAL PURSUANT TO 35 U.S.C. § 325(D) IS UNWARRANTED

As detailed in the Petition, the Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny institution in view of separate and complete consideration of both steps of *Advanced Bionics LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential). Patent Owner alleges that the Examiner already considered § 112(a) written description and enablement arguments against the challenged claims during prosecution of the '109 Patent and against family member application claims. Br., 36-45. In each case, however, the Examiner either (1) did not consider or did not reject the pending claims under § 112(a), (2) made written description and/or enablement rejections against materially different claims, or (3) committed material error in considering and allowing the pending claims in view of the fatal § 112(a) defects highlighted in the Petition. Each of these scenarios is detailed below, the sum total of which weigh heavily against discretionary denial under § 325(d).

A. Prosecution of the '109 Patent (App. No. 18/346,420)

1. *Advanced Bionics* Step 1: Whether the same or substantially the same prior art or argument previously was presented to the Office.

As noted in the Petition, the Examiner never rejected the challenged claims based on inadequate written description or lack of enabling disclosure. Pet. 18-20.

The Examiner's sole rejection of the pending claims during prosecution was for obviousness over the prior art as applied to the earliest claimed priority date of the '109 Patent. But the disclosure provided in the '420 Application (identical to the '767 Application, and encompassing the disclosures of each application in the priority chain of that application tracing back to the '840 JP Priority Application) fails to describe a single example falling within the genus of over 3,400 claimed options for producing a cascade of functional recombinant zymogen factors (Factors B, C, and Pro-clotting enzyme) to detect endotoxin. Pet. 18-20, 23-60.

While the Examiner looked for and applied prior art against these claims, the Examiner did not recognize that they were insufficiently described as of their priority date under 35 U.S.C. § 112. Therefore, the same or substantially the same written description and enablement arguments advanced in the Petition were not considered by the Examiner and were not overcome during prosecution. The Petition presents evidence never considered by the Examiner demonstrating that Patent Owner did not possess or enable the full scope of the claimed invention.

Petitioner points to the fact that an Examiner's proposed amendment late in prosecution of the '420 Application including the phrase "wherein the horseshoe crab Factor C is a *Tachypleus tridentatus* Factor C or a *Limulus polyphemus* Factor C" constitutes evidence that the Examiner considered the written description support and enablement of the challenged claims. Br., 43-44.

However, not only is there is no evidence that the Examiner considered whether there was support and or an enabling disclosure for this claim element, the § 112(a) arguments developed in the Petition and lodged against the challenged claims go well beyond whether this one claim limitation was supported and/or enabled by the disclosures leading back to the priority documents for the '109 Patent. The Petition argues that the claim as a whole lacks written description support and an enabling disclosure under 35 U.S.C. § 112(a). *See e.g.*, Pet. 26-29 (“[T]he assay of the claimed method [for challenged claims 1-9] can comprise all three proteins recombinantly produced in a certain CHO cell line, or all three proteins recombinantly produced in a certain HEK cell line, or with a variety of mix-and-matching proteins where Factor C is from the *Tachypleus tridentatus* [or *Limulus polyphemus*] species of crab and expressed in CHO [or HEK] cells, but Factor B and Pro-clotting enzyme is produced via any other mammalian expression system and from any other species of horseshoe crab. The result of these optional combinations is a claim that, even by a conservative estimate, broadly recites a genus of thousands of possible methods for producing the claimed endotoxin assay agent. Jain, ¶58. ... While the '109 patent inventors claimed a method for producing an endotoxin detection assay broadly encompassing thousands of possible options for assembling the claimed components thereof, they did not

describe in the '767 Application a single example of the making of such an assay.”).

Moreover, even as to this one limitation, it appears that the Examiner was misled or mistaken and therefore his suggestion to incorporate this limitation into the pending claim was material error (*see* Section III.A.2., *infra*).

2. *Advanced Bionics* Step 2: Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Patent Owner argues that “although the Examiner did not expressly reject the Challenged Claims for lack of written description and enablement ... he proposed some of the claim limitations Petitioner now argues lack written description and enablement support.” Br. 44. Even if this claim limitation proposal was found somehow to be substantially similar to the much more comprehensive § 112(a) arguments lodged in the Petition (against a claim with broad scope and no disclosure of a single example falling within such scope), this proposal was material error on the part of the Examiner—as demonstrated by both the prosecution history record and the same Examiner’s more recent rejection of the priority claim (for lack of written description and enablement) of nearly identical claims in a continuation application.

The Examiner amendment proposed with the Examiner Interview Summary on November 17, 2023 included, as Appendices, the submissions that Patent

Owner had provided to the Examiner. EX1002, 153-173. One of these submissions (Appendix B) was described in the Examiner Interview Summary as “experimental data” provided in support of Patent Owner’s prior suggested amendment. *Id.* at 153. That Appendix states, “In reference to ‘(2) *Expression of Factor C in Mammalian Cells (CHO DG44)*’ sections of the present specification and WO2018/074498A1, Factor C of *Limulus polyphemus* (LpFC) and *Tachypleus tridentatus* (TtFC) were recombinantly expressed in CHO DG44, CHO-K1, CHO-S and HEK293 cells.” *Id.* at 163.

Of course, as discussed extensively in the Petition and above, WO2018/074498 is a PCT **filed on October 18, 2017** where inventor Mizumura reported *finally* elucidating the zymogen protein sequences for *Limulus polyphemus* horseshoe crabs. EX1005, ¶0017 (“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, and have further discovered that these can be used for a variety of purposes, thereby completing the present invention.”). Given these dates, WO2018/074498 demonstrates that the ’109 Patent specification, whose filing dates back to December 10, 2013, ***could not have*** described or enabled the

later alleged accomplishment of recombinant expression of *Limulus polyphemus* Factor C.

The Examiner's recent rejection of near identical claims in the child '128 Application also demonstrates material error. *See* Section II.A.1, *supra*. *See also* EX1042, 2-6 ("The disclosures of the priority application nos. US 14/650,767 and PCT/JP2013/083082 fail to provide adequate descriptive support and enablement in the manner provided by 35 U.S.C. 112(a) ... [because] [n]either the instant application nor any of the priority applications discloses a working example of cloning and expression of *Limulus polyphemus* Factor C, Factor B, and Pro-clotting enzyme proteins from a HEK 293 cell").

For at least these reasons, the Board should refrain from exercising its discretion to deny the Petition and should instead give careful consideration to the merits of the Petition whose arguments are now also supporting the rejection of similar pending claims in this patent family.

B. Prosecution of U.S. Patent No. 11,236,318 (App. No. 16/399,386)

1. *Advanced Bionics* Step 1: Whether the same or substantially the same prior art or argument previously was presented to the Office.

As the Petition points out, while § 112(a) rejections were made in prior cases in the '109 Patent family, the subject claims in those families were distinct from

challenged claims 1-9 and the arguments made against those claims are inapplicable to claims 1-9. Pet., 19, n.4.

For example, in a June 30, 2020 Non-Final Rejection during prosecution of the ancestor '386 Application, the Examiner rejected claim 2 which was drawn to:

A Factor C protein having activity of Factor C,

wherein the Factor C protein comprises an amino acid sequence selected from the group consisting of:

(A) the amino acid sequence of SEQ ID NO: 2;

(B) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO:2, and having activity of Factor C;

(C) the amino acid sequence of SEQ ID NO: 4; and

(D) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence of SEQ ID NO:4, and having activity of Factor C,

wherein the Factor C protein is produced through being recombinantly expressed from a Chinese Hamster Ovary (CHO) DG44 cell or HEK cell, and

wherein the Factor C protein exhibits a residual activity of 10% or higher in the presence of 21 mM sodium citrate.

EX1040 ('386 FH), 515-516.

In that case, The Examiner correctly determined that the only disclosure of representative species in the specification was of “recombinant *Tachypleus*

tridentatus or *Carcinoscorpius rotundicauda* Factor C protein expressed in Chinese Hamster Ovary (CHO) cells or human embryonic kidney (HEK) cells, which Factor C protein has Factor C activity and contains (α -2,3)-linked terminal sialic acid in a greater amount as compared with a corresponding native horseshoe crab Factor C protein and/or a corresponding horseshoe crab Factor C protein recombinantly expressed using Sf9 as a host cell.” *Id.* at 374.

The Examiner also found that “[o]ther than [the above two disclosed species], there is no disclosed or art-recognized correlation between the structure of the recited Factor C protein and the characteristic of residual activity of 10% or higher in the presence of 21 mM sodium citrate and the additional characteristics recited in claims 3-9.” *Id.* at 375-76.

Finally, the Examiner concluded that “[i]n view of the limited disclosed structure-function correlation and the disclosure of only two representative species ... one of skill in the art would not accept the disclosure of a recombinant *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* Factor C protein expressed in Chinese Hamster Ovary (CHO) cells or human embryonic kidney (HEK) cells, which Factor C protein has Factor C activity and contains (α -2,3)-linked terminal sialic acid in a greater amount as compared with a corresponding native horseshoe crab Factor C protein and/or a corresponding horseshoe crab Factor C protein recombinantly expressed using Sf9 as a host cell as being

representative of other Factor C proteins as encompassed by the claims.” *Id.* at 376.

As Patent Owner acknowledges, the written description rejection of the pending claims “was based in large part on the residual activity limitation” (Br., 42) and was overcome by amending the claims to recite “wherein the Factor C protein contains (α -2,3)-linked terminal sialic acid in a greater amount as compared with a native horseshoe crab Factor C and/or a corresponding horseshoe crab Factor C protein recombinantly expressed using Sf9 as a host cell” (“the greater sialic acid limitation”), which was ultimately added *to all claims*. EX1040 (’386 FH), 227-231, 168-173. The residual activity limitation is not issue here.

Contrary to Patent Owner’s assertion (Br., 43), the Petition does not merely raise the same issue regarding written description support for an exceedingly large genus of known and unknown horseshoe crab Factor C sequences and whether they can be recombinantly expressed. The Petition argues that the disclosures in the continuity chain of challenged claims 1-9 (JP Priority Document and subsequent applications) do not describe or enable the *thousands of possible combinations of functional recombinant Factor C, Factor B, and Pro-clotting enzyme proteins* that are components of the claimed method of producing an endotoxin assay agent (including components recombinantly produced from the *Limulus polyphemus* horseshoe crab species). Pet. 9-11, 23-60. The instant

challenge is not the same nor substantially similar to the § 112(a) rejection lodged during prosecution of the '318 Patent.

The Examiner's grappling with scope and written description sufficiency for the claims of the '386 Application has no bearing on whether the Examiner was attuned to the written description and enablement issues presented in the Petition against later applied-for challenged claims 1-9. The Director should refrain from exercising her discretion so that these arguments (which the same Examiner is now applying to near identical claims) can be considered thoroughly by the Board.

2. *Advanced Bionics* Step 2: Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Patent Owner's emphasis on what the same Examiner did in prior applications in the continuity chain of the '109 Patent should apply equally to what the same Examiner has done in *subsequent applications* in this chain. As noted above, the *same* Examiner has determined that the priority date for similar claims is incorrect, and that the inventors did not describe or enable recombinantly produced *Limulus polyphemus* zymogen proteins in the priority document or identical specifications in the priority chain. EX1042, 6 ("In view of the noted disclosures of McClymont and Mizumura, one of skill in the art would have recognized that the disclosures of priority application nos. U.S. 14/650,767 and PCT/JP2013/083082, which were filed prior to the publications of McClymont and

Mizumura, *fail to adequately describe and enable cloning and expression of a polynucleotide encoding each of the L. polyphemus Factor C, Factor B, and Pro-clotting enzyme proteins from a HEK 293 cell.*”).

The Examiner’s failure to recognize this lack of § 112(a) support during prosecution of the challenged claims constitutes material error weighing heavily against discretionary denial.

C. Prosecution of U.S. 10,144,923 (App. No. 14/650,767)

1. *Advanced Bionics* Step 1: Whether the same or substantially the same prior art or argument previously was presented to the Office.

Patent Owner also points to prosecution of the great-grandparent application to the ’109 Patent (the ’767 Application) and written description and enablement rejections lodged against exceedingly broad, originally-filed claims in that ancestor application as somehow supportive of discretionary denial of the instant meritorious attack on claims 1-9. Br., 38-40. But discretionary denial should not be wielded simply because Patent Owner can find an extraordinarily broad original claim in an ancestor application that happened to draw an unrelated § 112(a) rejection nearly ten years earlier. Were that the case, a patent owner could prevent post-grant challenges to any continuation claims simply by drawing rejections to exceedingly broad claims early on in prosecution of an ancestor application.

In any case, the pending claims in the '767 Application were exceedingly broad and amended in ways that are immaterial to the flaws identified in the challenged claims. For example, as-filed claim 43 in the '767 Application recited “A horseshoe crab Factor C having activity of Factor C.” EX1058, 1. That claim arguably covers any active Factor C in existence (natural, recombinant, or otherwise). The Examiner recognized this and rejected that claim and dependent claim 47 accordingly:

In this case, the genus of claimed horseshoe crab Factor C polypeptides is widely variant, encompassing any horseshoe crab Factor C polypeptide expressed from any host cell and in view of the relative few disclosed representative species and the high level of unpredictability regarding the functionality, terminal sialic acid, residual activity in the presence of sodium citrate, molecular weight, amino acid sequence, and solubility, one of skill in the art would not accept the disclosure of Factor C isolated from *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda* hemocyte lysate and *Tachypleus tridentatus* Factor C expressed in Sf9 insect cells, CHO cells, or HEK cells as being representative of all other horseshoe crab Factor C polypeptides as encompassed by the claims.

EX1053, 8. The Examiner found the exceedingly broad claim 43 to be insufficiently supported by the disclosure of a few examples falling within this scope in the specification. *Id.*

What Patent Owner fails to point out is that it then ***amended*** claim 43 to include the greater sialic acid limitation, and amended claim 54 to recite mammalian expression (which was known to facilitate the additional of sialic acid using an α -2,3 linkage), and these amendments ***contributed*** to the Examiner's withdrawal of the § 112 rejection. EX2033, 60 ("Also, it was well-known in the prior art at the time of the invention that different cell types add a sialic acid to an expressed polypeptide using only a particular linkage, *e.g.*, Chinese Hamster Ovary (CHO) cells are only able to add sialic acid using an α -2,3 linkage (*see, e.g.*, paragraph 8 of Cottingham et al., US 2014/0249082, which has priority to 2010, cited on the IDS filed on 10/26/2016). As such, one of skill in the art would recognize that the specification in view of the state of the art at the time of the invention adequately describes and enables the full scope of the claimed horseshoe crab Factor C polypeptides."'). None of these arguments or amendments are at issue with the challenged claims.

Moreover, the claims that were ultimately allowed all incorporate the greater sialic acid limitation. *See* EX1059, cls. The allowed claims of the '923 Patent are distinct from challenged claims 1-9, which involve methods of generating endotoxin detection assay agents requiring the recombinant production of all three zymogen proteins (Factor C, Factor B, and Pro-clotting enzyme) in functional form and mixing and matching the same. EX1001, cls. The § 112 issues lodged and

addressed in during prosecution of the '923 Patent have no bearing on the Examiner's consideration of the patentability of the challenged claims.

2. *Advanced Bionics* Step 2: Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

In any case, and contrary to Patent Owner's argument in support of discretionary denial (Br., 39), the Examiner's statement that "Recombinant expression of Factor C polypeptides of ... *Limulus polyphemus* ... were well-known at the time of the invention" (EX2033, 60) was wrong and constituted a material error weighing *against* discretionary denial.

As of September 16, 2016, neither the gene nor amino acid sequences for *Limulus polyphemus* Factor C—from which recombinant expression could be achieved—had been elucidated, as the inventors themselves told the Patent Office (and the world) several years later. EX1005, ¶¶0010-12 ("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. ... in *Limulus polyphemus*, even though more than 20 years have passed since the report in the genus *Tachypleus*, complete identification of these proteins and genes in terms of both structure and function has not been achieved."). The Examiner now recognizes that recombinant expression of Factor C from *Limulus polyphemus* was not well-known as of December 10, 2012. EX1042, 2-6. This recent recognition

and claim rejection demonstrates that the Examiner's prior statement and allowance based on the same constituted material error.

D. Prosecution of U.S. 10,982,202 (App. No. 15/983,725)

1. *Advanced Bionics* Step 1: Whether the same or substantially the same prior art or argument previously was presented to the Office.

Finally, Patent Owner points to § 112(a) rejections during prosecution of the grandparent application to the '109 Patent as supporting discretionary denial. Br., 40-42. Again, all of the allowed claims from the '725 Application recite the greater sialic acid limitation, relate to the recombinant production of Factor C only, and require that the Factor C "has no peptide added to the N-terminus of Factor C." EX1060, cls. The prior §112 rejections have no bearing on whether the Examiner considered the arguments advanced in the Petition as to challenged claims 1-9. The Petition's meritorious challenge to such claims should not be discretionarily denied.

2. *Advanced Bionics* Step 2: Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

As noted above, the challenged claims are similar to the currently rejected claims of the '128 Application, where the Examiner has recognized that such claims are not entitled to claim priority to their earliest claimed effective filing dates (based on disclosures encompassed by and identical to the later specifications filed in the '109 Patent's continuity chain) because those disclosures do not

support or enable the full scope of such claims. EX1042, 2-6. Even if it is found that the allowance of the challenged claims was based on arguments similar to the Examiner's consideration of arguments in the '725 Application, (which Petitioner disputes, *see* Section III.D.1., *supra*), the Examiner's current rejection in the '128 Application lays bare the material error of the Examiner's allowance. The Director should decline to exercise its discretion in view of this material error.

IV. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Board decline to exercise its discretion in denying institution and instead refer consideration of challenged claims 1-9 to the merits panel for further review.

Respectfully submitted,
Charles River Laboratories, Inc.

Date: June 11, 2025

/Scott A. McKeown/

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing
**PETITIONER'S OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF** contains 11,996 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: June 11, 2025

/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 June 11, 2025, 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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