

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

PATENT OWNER'S DISCRETIONARY DENIAL BRIEF

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TABLE OF EXHIBITS

Exhibit No.	Description
2001	Disclaimer of Claim 10 in U.S. Patent 11,959,109
2002	Muta, et al., "Horseshoe Crab Coagulation Factor B, A Unique Serine Protease Zymogen Activated by Cleavage of an Ile-Ile Bond," (1993) J. Biol Chem., Vol. 268, No. 28, 21384-88 (1993)
2003	Muta, et al., "Proclotting Enzyme from Horseshoe Crab Hemocytes, cDNA Cloning, Disulfide Locations, and Subcellular Localization," (1993) J. Biol Chem., Vol. 265, No. 36, 22426-33
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition to European Patent No. 3530670
2005	Novitsky, T.J., "Biomedical Applications of Limulus Amebocyte Lysate," in , J. Tancredi et al (eds.), <i>Biology and Conservation of Horseshoe Crabs</i> , Springer Science+Business Media, LLC (2010) pp. 315-329
2006	Notice of Opposition to European Patent No. 3530670
2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466

2009	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 17/650,803
2010	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/275,777
2011	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/953,525
2012	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3530670
2013	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in Opposition to European Patent No. 3441466
2014	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 17/650,803

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2015	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/275,777
2016	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/953,525
2017	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in Opposition to European Patent No. 3441466
2018	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 17/650,803
2019	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/275,777
2020	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/953,525
2021	U.S. Patent Application Publication No. US 2023/0258647 A1
2022	Thorne, et al., "Evaluation of the <i>Limulus</i> Amebocyte Lysate and Recombinant Factor C Assays for Assessment of Airborne Endotoxin," Appl. Environ. Microbiol. 76(15):4988-95 (2010)
2023	International Publication Number WO 2012/118226
2024	Ding, J.L. and Ho, B., "Endotoxin detection – from <i>Limulus</i> Amebocyte Lysate to Recombinant Factor C," pp. 187-208 (2010)

2025	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in Opposition to European Patent No. 3441466
2026	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 17/650,803
2027	Tamura, H., " <i>EC Bacteriol. Virol. Rsch.</i> 2016," available at https://ecronicon.net/assets/ecbvr/pdf/ECBVR-01-ECO-03.pdf
2028	U.S. Patent No. 6,391,570
2029	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in Opposition to European Patent No. 3441466
2030	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 17/650,803
2031	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/275,777

2032	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/953,525
2033	Excerpt from U.S. Application No. 14/650767 (file history for U.S. Patent No. 10,144,923)
2034	Excerpt from U.S. Application No. 15/983725 (file history for U.S. Patent No. 10,982,202)
2035	Notice of Opposition to European Patent No. 3441466
2036	D19, "A comparison of <i>Limulus</i> Factor C expressed with and without terminal sialic acid glycosylation"
2037	Iwanaga, S., "The limulus clotting reaction" (1993) Curr. Op. Immunol., 5(1):74-82
2038	Iwanaga, S., "Primitive Coagulation Systems and their Message to Modern Biology" (1993) Thromb. Haemost., 70(01):48-55
2039	Iwanaga, S. et al., "New Types of Clotting Factors and Defense Molecules Found in Horseshoe Crab Hemolymph: Their Structures and Functions" (1998) J. Biochem., 123:1-15
2040	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in Opposition to European Patent No. 3441466

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2041	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 17/650,803
2042	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/275,777
2043	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/953,525
2044	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/275,777
2045	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/953,525
2046	U.S. Patent No. 10,473,663

I. INTRODUCTION

Pursuant to 37 C.F.R. § 42.207 and the March 26, 2025 Memorandum regarding Interim Processes for PTAB Workload Management from the Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the USPTO (“Process Memorandum”), Patent Owner Seikagaku Corp. (“Patent Owner” or “SKK”) submits this brief in support of its request for discretionary denial of the Petition for Post-Grant Review of Claims 1-10 of U.S. Patent No. 11,959,109 (“the ’109 Patent”) (EX1001) filed by Petitioner Charles River Laboratories (“Petitioner” or “CRL”). This submission addresses applicable bases for discretionary denial of institution according to guidance provided in the Process Memorandum. Patent Owner has disclaimed claim 10, (EX2001), therefore only claims 1-9 are at issue.

Petitioner relies on assertions that (i) claims 1-9 (“Challenged Claims”) lack written description, (ii) the Challenged Claims lack enablement, and (iii) given the lack of written description or enablement, the Challenged Claims are only entitled to a July 3, 2023 priority date, rather than the December 10, 2013 filing date of PCT/JP2013/083082. Based on the July 3, 2023 priority date, Petitioner argues that another patent publication from Patent Owner, U.S. Publication No. 2019/0241629 (“the ’629 Application”) (EX1015), anticipates the Challenged Claims. Pet. at 1-6.

The Director should exercise her discretion and deny institution.

First, Petitioner has failed to show that the '109 Patent is eligible for PGR. The '109 Patent claims priority to a Japanese patent application filed on December 10, 2012, JP2012-269840 (“the '840 JP Priority Application”) (EX1008). Petitioner's primary argument that the '109 Patent is PGR-eligible is a non-binding transition application statement. Petitioner also argues that the '840 JP Priority Application fails to provide sufficient § 112 support for the Challenged Claims. However, these arguments, like Petitioner's unpatentability arguments, are based on improperly importing components into the Challenged Claims. Thus, Petitioner has failed to meet its burden of showing the '109 Patent is eligible for PGR.

Second, Petitioner's written description and enablement arguments are directly contrary to Petitioner's statements made in other public documents, including in its own patent filings and publications, and adversarial proceedings.¹ Those admissions establish, the art of cloning and expressing proteins was well-

¹ Patent Owner's arguments here are consistent with arguments and an expert declaration submitted in a Notice of Opposition against one of its European patents in a different family. As discussed further below, the evidence shows those Opposition papers were likely filed by Petitioner. If correct, Petitioner has taken starkly inconsistent positions before the Board and the European Patent Office. That should be a basis for both discretionary denial and denial on the merits.

established as of December 2012, and the mechanisms underlying the widely used horseshoe crab coagulation cascade endotoxin detection assays were well-characterized.

Third, Petitioner's arguments regarding lack of written description support and lack of enablement are the same or substantially the same as arguments previously presented to the Office in the prosecution histories of related family member patents concerning the same issues raised in the Petition. Petitioner omits nearly the entirety of the Examiner's intensive consideration of written description and enablement in those file histories, addressing only one such rejection in a conclusory and inaccurate footnote. Petitioner therefore has not shown any error by the Office, much less a material one. Accordingly, the Board should exercise its discretion under § 325(d) and deny institution.

II. OVERVIEW OF THE '109 PATENT

The '109 Patent is titled "Recombinant Factor C and Method for Producing the Same, and Method for Measuring Endotoxin." EX1001. Independent claim 1 of the '109 Patent, the sole independent claim after Patent Owner's disclaimer of claim 10, is directed to a method for producing an endotoxin assay agent comprising a horseshoe crab proteins Factor C, Factor B, and pro-clotting enzyme expressed by mammalian cells.

The '109 Patent issued from U.S. Patent Application No. 18/346,420, which is a continuation of U.S. Patent Application No. 17/554,128, filed December 17, 2021, which is a continuation of U.S. Patent Application No. 16/399,386 (issued as U.S. Patent No. 11,236,318), filed April 30, 2019, which is a continuation of U.S. Patent Application No. 15/983,725 (issued as U.S. Patent No. 10,982,202), filed May 18, 2018, which is a continuation of U.S. Patent Application No. 14/650,767 ("the '767 Application," which issued as U.S. Patent No. 10,144,923), filed June 9, 2015, which is a National Stage Entry of PCT/JP2013/083082, filed December 10, 2013. The '109 Patent further claims foreign priority to JP 2012-269840, filed on December 10, 2012.²

Endotoxin is a lipopolysaccharide present in the outer membrane of Gram-negative bacteria that "even a very small amount... causes various pathological conditions" following "bacterial infection." EX1001 at 1:40-42. Detection of endotoxin is essential for establishing the safety of injectable pharmaceutical

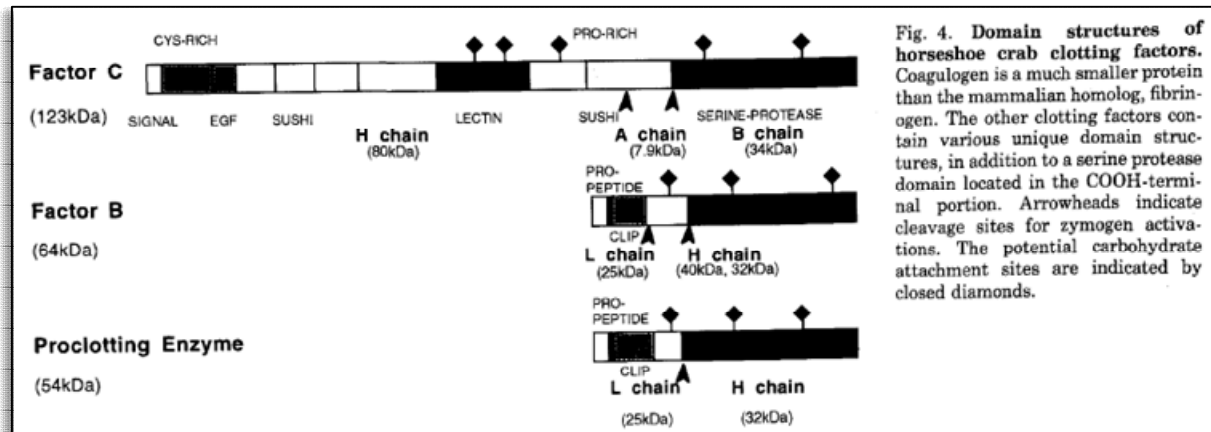
² Petitioner argues that the claims are not entitled to an effective filing date of earlier than December 10, 2013. Pet. at 10. Patent Owner's arguments in this preliminary response are based on the December 10, 2013 priority date applied by Petitioner. Patent Owner is not waiving any arguments that the Challenged Claims are entitled to an earlier priority date.

products and medical devices. *Id.* at 1:45-47. Factors contained in amebocyte lysate of horseshoe crabs have been used to measure endotoxin for decades. *Id.* at 1:52-61 (citing EX2037). These methods employ a cascade reaction that is triggered by endotoxin and involves activation of three serine proteases named Factor C, Factor B, and Pro-clotting enzyme found in the lysate. *Id.* at 1:61-2:12 and Fig. 1; *see also* EX2037 at 1.

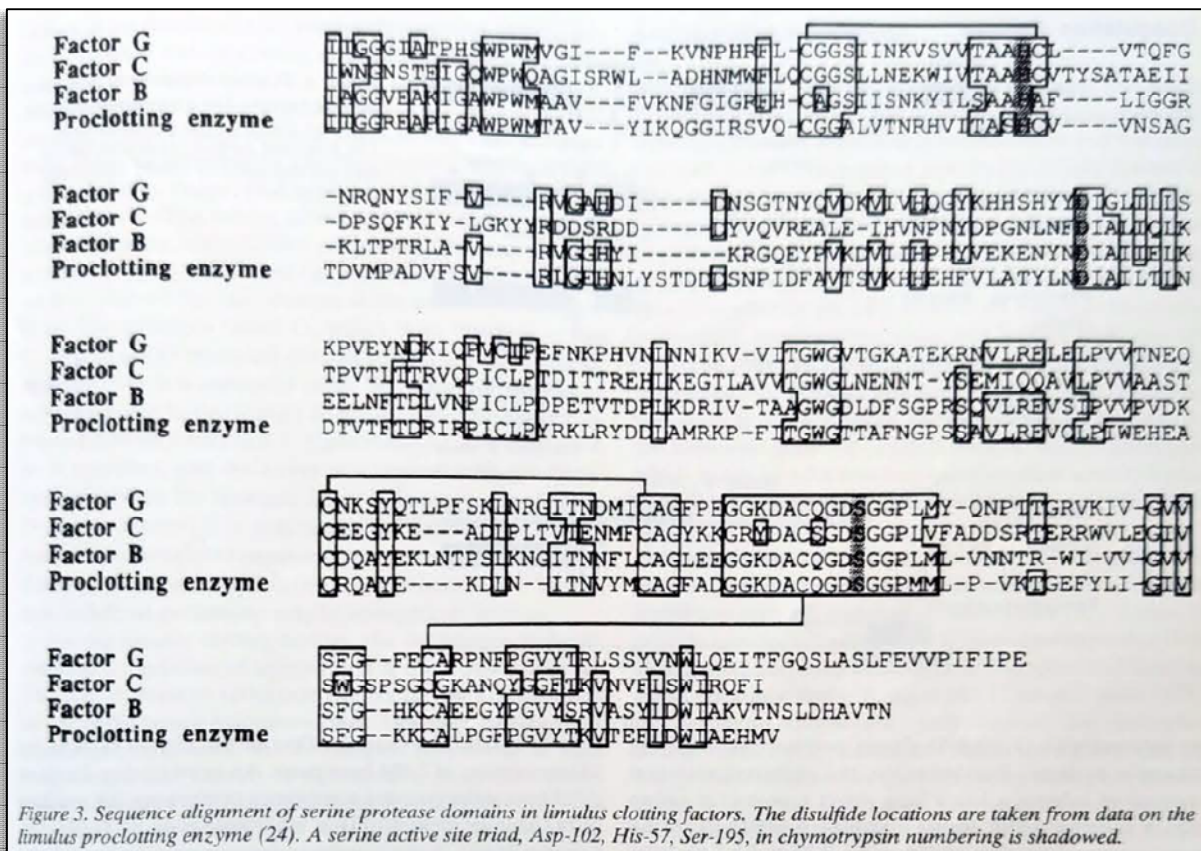
There are four living species of horseshoe crab: *Tachypleus tridentatus*, *Limulus polyphemus*, *Carcinoscorpius rotundicauda*, and *Tachypleus gigas*, all of which have similar morphological characteristics and physiological coagulation systems. EX1001 at 13:58-62. The components of the cascade reaction in three of these four species have been extensively studied. For example, the gene and amino acid sequences of Factor C proteins from *T. tridentatus* and *C. rotundicauda* were published in 1991 and 1998, respectively. EX1003 (Jain Decl.) ¶ 37 (citing EX1009 and EX1010). Factor C protein from *L. polyphemus* was isolated and biochemically characterized in 1991. EX1025. This 1991 publication also reported a partial amino acid sequence, although the full DNA and amino acid sequence of *L. polyphemus* was not publicly disclosed until 2017.

Factor B and Pro-clotting enzyme from *T. tridentatus* were cloned and sequenced in 1993 and 1990, respectively. EX2002; EX2003. Factor B and Pro-clotting enzyme are similar to each other in terms of amino acid sequence and

structure, each containing a clip domain and serine protease domain. EX2038 at 3-4; EX2039 at 2-3 and Fig. 4 (reproduced in relevant part below):



Factor B and Pro-clotting enzyme also share significant sequence homology with the serine protease domain of Factor C, with all 3 factors having an identical serine protease active site triad. EX2038 at Fig. 3 (reproduced below):



Not only was it known in the art that the structure and biochemistry of these three proteins were highly similar across horseshoe species, it was also known in the art that the horseshoe crab coagulation system was indistinguishable in terms of their function. *See, e.g.*, EX1025 at 153 (“These findings also lead to the idea that the hemocytes of *L. polyphemus* probably contain a coagulation system similar to that established for the *T. tridentatus* hemocytes.”); *see also* EX2005 at 2 (stating LAL [*Limulus* amebocyte lysate] can be obtained from *L. polyphemus* and *T. tridentatus* and can also be obtained from the other two species) and Fig. 2 (“consensus biochemistry”); EX2022 at 7 (reporting that *L. polyphemus* lysate and recombinant

C. rotundicauda Factor C showed “a very strong positive correlation” and “returned similar values” in quantitative endotoxin detection assays).

Patent Owner reported that recombinant Factor C from *C. rotundicauda* and recombinant Factor B and Pro-clotting enzyme from *T. tridentatus* could be used to reconstruct the endotoxin detection cascade. EX2023 ¶ 9 (citing WO 2008/004674). Thus, it was known in the art as of December 2013 that the endotoxin-detecting function of the cascade was preserved even when proteins from different species were used.

Assays using *Limulus* amebocyte lysate (“LAL”) to detect endotoxin have been used since the 1970s, leading to concerns that over-harvesting of horseshoe crab species in Asia and America may drive these organisms to potential extinction. EX2024 at 12-13. Use of recombinant proteins provides an unlimited source of the horseshoe crab coagulation factors and thus avoids the need to capture and bleed horseshoe crabs to make the amebocyte lysate. EX1001 at 2:26-34. There was also a desire to increase the sensitivity compared to and reduce the potential for lot-to-lot variations in amebocyte lysate-based assays. EX2024 at 12.

A commercial product employing recombinant *C. rotundicauda* Factor C was commercially launched in 2004. *Id.* at 16 (discussing PyroGene); *see also* EX2023 ¶ 10. A fully recombinant assay using Factor C, Factor B, and Pro-clotting enzyme expressed in insect cells was also known as of 2013. EX1001 at 2:36-39 (citing WO

2008/004674 and EX2023 (WO 2012/118226)). A fully recombinant assay based on the cascade reaction was marketed by Patent Owner as PyroSmart™. EX2027 at 1. However, such recombinant assays suffered from reduced residual activity in the presence of ions found in many injectable pharmaceutical or medical formulations, which interfered with the detection of endotoxin.

The '109 Patent inventors discovered Factor C expressed from mammalian cells had higher residual activity in the presence of salt ions relative to native Factor C and Factor C expressed in insect cells. EX1001 at 3:25-30, 35:58-36:3.

This discovery was significant because “injections [of medicines] administered in vivo generally contain a variety of salts (ions)” and yet injectable products require the greatest sensitivity in terms of endotoxin detection for safety. EX1001 at 3:13-20.

III. PERSON OF ORDINARY SKILL IN THE ART AND CLAIM CONSTRUCTION

Petitioner proposes a high level of ordinary skill in the art, namely a person with “a Ph.D. degree in biological, chemical or biochemical engineering, molecular biology, or biochemistry and at least two years of experience in the field of utilizing or assessing horseshoe crab zymogen proteins (lysate, purified native and/or recombinantly produced) for endotoxin detection and quantitation.” Pet. at 22.

According to Petitioner, more education could substitute for experience to a certain extent, and vice versa. *Id.*

Solely for purposes of this Preliminary Response, Patent Owner does not dispute Petitioners' definition of a person of ordinary skill in the art ("POSA"). Patent Owner reserves the right to present a different definition of a POSA in these proceedings, should the Board institute trial, and any other proceedings regarding the '109 Patent.

Petitioner does not argue that any terms require construction. For purposes of this Preliminary Response only, Patent Owner agrees that the terms can be afforded their plain and ordinary meaning.

IV. PETITIONER HAS NOT SHOWN ELIGIBILITY FOR POST-GRANT REVIEW

It is Petitioner's burden to establish the '109 Patent is eligible for post-grant review. *See Commonwealth Scientific & Indus. Res. Org. v. BASF Plant Science GmbH*, No. PGR2020-00033, Paper 11 at 7 (P.T.A.B. Sept. 10, 2020). The post-grant review provisions of the Leahy-Smith America Invents Act ("AIA") apply only to patents subject to the first-inventor-to-file provisions of the AIA. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 6(f)(2)(A), 125 Stat. 284 (2011). For a patent that issues from a "transition application," that is, an application filed on or after March 16, 2013, that claims the benefit of an earlier filing date, MPEP

§ 2159.04.3, eligibility for post-grant review depends on whether a priority application filed before March 16, 2013 provides adequate written description and enabling support for the challenged claims.

A. The Transition Statement is Not Determinative

Petitioner relies on a “Statement Under 37 C.F.R. § 1.55 or § 1.78 for AIA (First Inventor to File) Transition Applications” (EX1022) submitted during prosecution of an application in the '109 Patent's priority chain. Pet. at 9. However, Petitioner makes no showing that this transition statement made in a “great grand-parent application” applies to any specific feature of the Challenged Claims. Transition statements are revocable (MPEP § 210.III(A)) and must be weighed “against the other evidence” submitted in a proceeding. *Paice LLC v. Toyota Motor Corp.*, 504 F.3d 1293, 1312 (Fed. Cir. 2007); *accord Shell Oil Co. v. United States*, 896 F.3d 1299, 1312 (Fed. Cir. 2018).

B. The Challenged Claims are Supported by the '840 JP Priority Application

Petitioner argues that the '840 JP Priority Application does not describe or enable the challenged claims. However, Petitioner's arguments are based on improperly importing limitations into Claim 1 and therefore cannot carry its burden to show the '109 Patent is PGR-eligible.

1. Petitioner improperly imports limitations into Claim 1

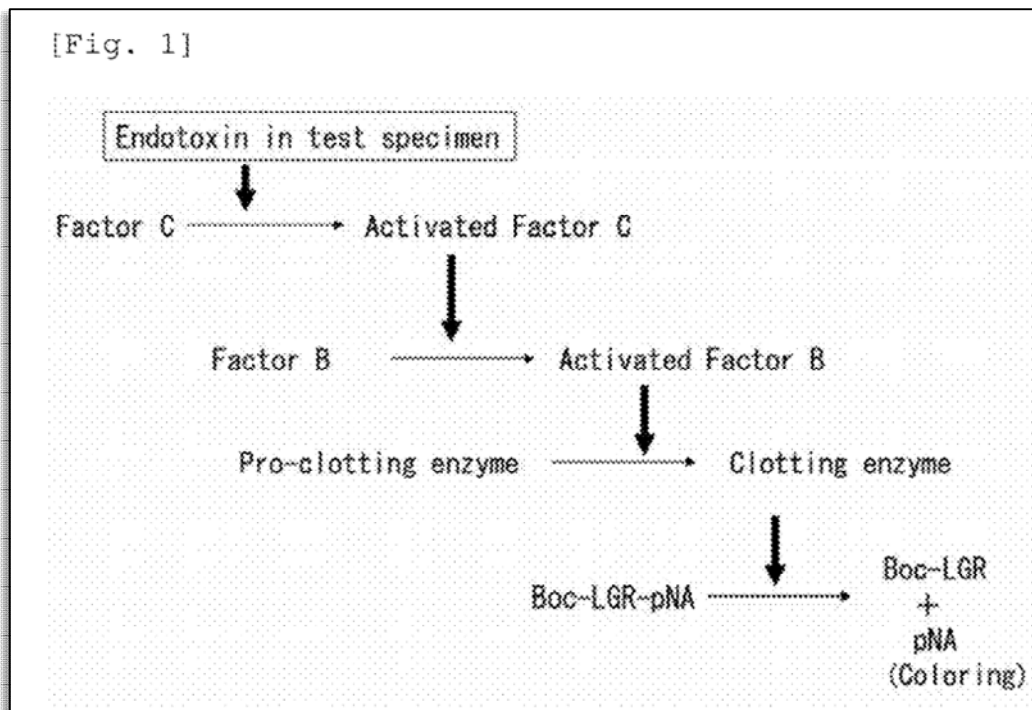
Petitioner's arguments that the '840 JP Priority Application fails to provide sufficient written description and enablement of the Challenged Claims rely on the premise that the Claim 1 requires the steps of mixing with a test specimen and that a cascade reaction occur.

For example, Petitioner argues that “an adequate written description would have to either disclose representative examples of the possible *working cascades* of various proteins or some accurate structural feature of the claimed proteins that allow them to *function in the claimed assay as a whole*.” Pet. at 35 (emphasis added). Petitioner extensively criticizes the specification for failing to describe ways of making or producing “a functioning endotoxin detection assay” or “making an endotoxin detection assay... to act in a functioning cascade for the detection of endotoxin.” *Id.* at 25, 29, 31, 32, 34, 36; *see also id.* at 33 (“a functioning enzymatic cascade to detect endotoxin as claimed”).

Petitioner's enablement arguments are based on the same premise—that Claim 1 requires the additional steps associated with using the endotoxin assay agent produced by the recited steps. *See, e.g.,* Pet. at 40 (arguing that a POSA would have to “engage in random trial-and-error discovery to assemble functional claimed assays”); *see also id.* at 41 (“all of the challenged claims require that the claimed combination of recombinantly produced proteins result in a functional assay”), 43

(“functioning endotoxin assay agent” or “functioning endotoxin assay”), 44 (“work as a cascade”), 46 (components must be “able to detect endotoxin”), 48 (“functioning endotoxin-detection assay”) and 50 (claims require a “functional assay capable of detecting endotoxin”).

Claim 1 is directed to a method for producing an endotoxin assay agent. Claim 1 *does not require* the agent to be combined with a test specimen and a detection substrate, or that a coagulation cascade take place—all of which would be required to use the agent to measure endotoxin. All that Claim 1 requires is the expression of functional Factor C protein from two of the four species of horseshoe crab into the culture supernatant by Chinese Hamster Ovary or Human Embryonic Kidney cells, expression of functional Factor B and Pro-Clotting enzyme in mammalian cells and producing an endotoxin assay agent comprising these three proteins. Notably, the resulting endotoxin assay agent would produce a cascade reaction only *after* it is mixed with an endotoxin-containing test specimen and a detection substrate. *See, e.g.*, EX1001 at 1:66-2:21; *see also* EX1001 at Fig. 1, below:



But these additional components and steps are not recited in Claim 1. The entire premise of Petitioner's argument is based on improperly importing these components and steps and an ensuing cascade reaction, into Claim 1.

A comparison of Claim 1 and claim 10, which Patent Owner has disclaimed illustrates Petitioner's fundamental error:

Claim 1	Claim 10
A method for <u>producing an endotoxin assay agent</u> comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising: 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, expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell, expressing the horseshoe crab Pro-clotting enzyme having activity of Proclotting enzyme in a mammalian cell as a host cell, and producing an endotoxin assay agent comprising the horseshoe crab Factor C, the	A method for <u>measuring endotoxin</u> in a test specimen, the method comprising: 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, expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell, expressing the horseshoe crab Pro-clotting enzyme having activity of Proclotting enzyme in a mammalian cell as a host cell, and producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-

horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme, 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.	clotting enzyme, mixing the endotoxin assay agent and a test specimen, and <u>measuring progress of a cascade reaction,</u> 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.
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Claims 1 and 10 are similar, but the language of Claim 10 clearly sets forth the additional steps require for using the endotoxin assay agent to measure endotoxin, which include mixing with a test specimen and measuring a cascade reaction. In contrast, Claim 1 does not include either of those limitations. “[W]hen a patent claim ‘does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim in determining either validity or infringement.’” *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1326 (Fed. Cir. 2003) (declining to read limitation directed to use of exogenous DNA into claim where a different claim expressly included that limitation).

While the endotoxin assay agent resulting from the method of Claim 1 is intended for use in an endotoxin detection assay, Claim 1 is not directed to carrying

out such an assay to detect endotoxin. For example, the specification makes clear that both mixing with a test specimen containing endotoxin and addition of a detection substrate are required for a “functioning endotoxin detection assay.” *See* EX1001 at 24:14-20, 25:9-15, 26:4-49. There is no basis in the language of Claim 1 to import these additional components and steps from the specification as Petitioner has done. *Amgen Inc.*, 314 F.3d at 1325 (“The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim.”).

Because Petitioner's argument that the '109 Patent is PGR-eligible because Challenged Claims are not entitled to the effective filing date of the '840 JP Priority Application is based on a flawed premise, it should be rejected. For the same reason, Petitioner's arguments that the Challenged Claims are invalid miss the mark, providing an additional reason for the Director to deny institution.

2. The '840 JP Priority Application describes and enables the Challenged Claims

Petitioner argues that there is no support for: 1) recombinantly producing Factor B or Pro-clotting enzyme in mammalian cells, and 2) generating an assay agent with three functional recombinantly produced proteins expressed via different mammalian cell lines or with sequence information from different species according to challenged claim 1. Pet. at 10-11. As Petitioner acknowledges, the application

that matured into the '109 Patent is a transition application because it was filed after March 16, 2013, but claims benefit of an application that was filed before that date. Specifically, the '109 Patent claims priority to a Japanese patent application filed on December 10, 2012, JP2012-269840 (“the '840 JP Priority Application”). Pet. at 8. Under a correct reading of the claims, contrary to Petitioner's argument, these elements are described and enabled by the '840 JP Priority Application.

First, with respect to recombinantly producing Factor B or Pro-clotting enzyme in mammalian cells, the '840 JP Priority Application states that “[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*.” EX1008 at 13 (¶ 0052) (emphasis added). The '840 JP Priority Application provides general instructions regarding expressing factor C in mammalian cells as well as working examples of expressing Factor C in CHO DG44 and HEK293 cells, which are mammalian cells. EX1008 at 11, 18-19 (¶¶ 0036-0037, 0101-0109). Petitioner has not provided any evidence that the techniques in these examples for expressing Factor C could not be “applied correspondingly” to expressing Factor B and Pro-clotting enzyme. Further, there were no known issues in the art with expressing Factor B and Pro-clotting enzyme in mammalian cells. EX1008 at 21 (¶ 0126). Thus, expressing Factor B

and Pro-clotting enzyme in mammalian cells is both described and enabled by the '840 JP Priority Application.

Second, with respect to generating the assay agent of claim 1 with three functional recombinantly expressed proteins from different species of horseshoe crab, the '840 JP Priority Application states that “the factor B of the present invention is a factor B derived from horseshoe crab” and the “pro-clotting enzyme of the present invention is a pro-clotting enzyme derived from horseshoe crab” and identifies the four species of horseshoe crab as “[e]xamples of horseshoe crabs.” EX1008 at 12 (¶ 0041).

The '840 JP Priority Application goes on to state that “the factor C of the present invention, the factor B of the present invention, and the pro-clotting enzyme of the present invention may construct [sic] expression cells for each factor and express them separately.” EX1008 at 14 (¶ 0063). The '840 JP Priority Application also provides 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. EX1008 at 21 (¶¶ 0122-0125).

Thus, contrary to Petitioner's assertion (Pet. at 10-11) the '840 JP Priority Application also describes and enables the methods of producing the endotoxin assay agents of Claim 1.

The '840 JP Priority Application also describes and enables the methods of Claims 2-9, which depend from Claim 1.

Claims 2 and 3 require the mammalian cell expressing Factor B (Claim 2) or Pro-clotting enzyme (Claim 3) is a Chinese Hamster Ovary ("CHO") cell or a Human Embryonic Kidney ("HEK") cell. As discussed above, the '840 JP Application describes methods of producing Factor C in CHO DG44 and HEK293 cells, and states that these methods "can be applied correspondingly" to Factor B and Pro-clotting enzyme. EX1008 at 12, 18-20 (¶¶ 0042, 0101-0111). Claim 4 requires the Factor B and Pro-clotting enzyme be "selected from the group consisting of *Tachypleus tridentatus* and *Limulus polyphemus*." As discussed above, the specification discloses these two species as examples of horseshoe crabs that are sources of the Factor B and Pro-clotting enzyme proteins of the present invention. EX1008 at 12 (¶ 0041).

Claims 5-7 recite additional limitations concerning the Factor C protein using in the method of claim 1. Claim 5 requires the Factor C to "contain[] (α -2,3)-linked terminal sialic acid in a greater amount, as compared with a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell." Claim 6 recites a range of molecular weight for Factor C determined by a specified method. Claim 7 requires "filtering the culture supernatant comprising the horseshoe crab Factor C." Each of these additional limitations is disclosed and enabled by the '840 JP Priority

Application. EX1008 at 6-7, 19-21, 105 (¶¶ 0017, 0019, 0106, 0109, 0118-0121 and Fig. 2)

Claim 8 recites an additional limitation that “the endotoxin assay agent is formulated as solid, liquid, or gel.” This is disclosed and enabled by the '840 JP Priority Application. EX1008 at 15 (¶ 0069).

Finally, claim 9 recites that the three proteins “are separately expressed in individually established host cells.” This is also disclosed and enabled by the '840 JP Priority Application. EX1008 at 13, 14 (¶¶ 0054, 0063).

For the above reasons, Petitioner has not met its burden of establishing the '109 Patent is eligible for PGR. The Director should deny institution.

V. THE DIRECTOR SHOULD EXERCISE HER DISCRETION AND DENY INSTITUTION

A. The Director Should Deny Institution Because Petitioner's Arguments are Inconsistent with Its Statements Outside of the Petition

The Director should exercise her discretion and deny institution because Petitioner appears to have submitted an expert declaration and made arguments to the European Patent Office in opposing Petitioner's EP 3530670 B1³ (“EP '670”)

³ This EP patent claims priority to PCT/JP2017/037629, the '629 Publication the Petition argues is prior art to and anticipates the Challenged Claims. Pet. at 61.

that are *directly contradictory to its arguments in the Petition*. And statements made in Petitioner's own patents are inconsistent with its positions here. If standing alone these contradictory positions do not warrant discretionary denial, Petitioner's contradictory positions still bear on the Director's decision. *See* Process Memorandum at 2.

For example, routine discovery under 37 C.F.R. § 42.51(b)(1) requires disclosure of such inconsistent information. 37 C.F.R. § 42.51(b)(1)(iii). Accordingly, the Board could only view Petitioner's arguments here with extreme skepticism, if not disregard them altogether, rendering Petitioner's unpatentability challenge exceedingly weak.

1. Arguments in the Opposition

With respect to written description, Petitioner argues that “the '109 Patent inventors did not and *could not have* described an example of these proteins from *Limulus polyphemus* for the claimed assay because the gene and sequence information for Factor C, Factor B, and Pro-clotting enzyme for *Limulus polyphemus* horseshoe crabs was not yet disclosed as of the claimed priority date of the '109 Patent.” Pet. at 31 (emphasis added); *see also* Pet. at 43 (“a POSA would not have been able to make or use (as of 2013) and without undue experimentation” the combinations allegedly encompassed by claim 1 “into a functioning endotoxin agent.”).

These assertions are contradicted by arguments made in a Notice of Opposition and supporting expert declaration filed against Patent Owner's EP '670 on November 22, 2024 ("the EP '670 Opposition"). In the EP '670 Opposition papers, the Opponent agreed with the arguments Patent Owner submitted during prosecution of the '767 Application, namely, that "it is a matter of routine practice for a person skilled in the art to determine the sequence of a known protein." EX2006 ¶ 59 (emphasis in original). The Opponent argued, as Patent Owner does here, that "the skilled person merely had to carry out the teaching of [the '767 Application] using standard techniques to arrive" at the full sequence of *L. polyphemus* Factor C. *Id.* ¶ 36. The EP '670 Opposition papers included an expert declaration by Professor Michael A. Frohman ("Frohman Declaration") (EX2004) supporting these arguments. EX2006 ¶ 33.

While the identity of the filer of the EP '670 Opposition is not expressly disclosed, substantial evidence indicates that ***Petitioner is the Opponent*** and is thus responsible for the submission of the EP '670 Opposition papers, including the factual statements and opinions made in the Frohman Declaration.

a. Evidence indicates that the Opposition papers were submitted on Petitioner's behalf

Sandra Pohlman from the law firm df-mp Dörries Frank-Molnia & Pohlman submitted the Notice of Opposition to EP '670 and Frohman Declaration. EX2006

at 1. She also currently handles prosecution for Petitioner's European Patent Application EP 4291648, titled "Hybrid Amebocyte Lysate and Uses thereof" as she is listed as the "Representative(s)." EX2007.

As part of the EP '670 Opposition, Ms. Pohlman and her firm submitted a document D24 by Jeak Ding and M. Anthony A. Navas III entitled "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, *Carcinoscorpius rotundicauda*" ("*Ding*") in the EP '670 Opposition, which included a watermark and unique identifier of "COM04X01498" (reproduced below):



EX2012 at 1 (annotated).

Notably, the *exact same watermark and unique identifier* appear in copies of *Ding* submitted by Petitioner during prosecution of its U.S. Application Nos.

17/650,803 (EX2009), 18/275,777 (EX2010), and 18/953,525 (EX2011). That a reference with the same watermark and unique identifier appears not only in the EP ’670 Opposition but also in the file histories of applications prosecuted by Petitioner strongly suggests that Petitioner and the Opponent of EP ’670 are one and the same.

Ms. Pohlman also submitted an Opposition against Patent Owner’s European Patent No. 3441466 (“EP ’466 Opposition”), which claims priority to the ’840 JP Priority Application, and is in the same patent family as the ’109 Patent. EX2035. The same distinctive characteristics discussed above also appear in the copy of *Ding* submitted with the EP ’466 Opposition. EX2008. In addition to *Ding*, Ms. Pohlman and her firm submitted four other references that have ***identical markings*** (e.g., watermarks, translations, handwritten notations) to documents filed by Petitioner as part of prosecution of U.S. Application Nos. 17/650,803, 18/275,777, and 18/953,525, which are applications filed by Petitioner and concern amebocyte lysates containing recombinant clotting factors and their use for detecting endotoxins in a sample. These matching characteristics are described in the table below.

Document	Matching characteristics	Filed in	Filed by
Wang et. al. 2002	Vertical watermark: “Downloaded from	EP ’466 Opposition (EX2013)	df-mp Dörries Frank-

	[website] by guest on March 28, 2020”		Molnia & Pohlman
		U.S. App. No. 17/650,803 ⁴ (EX2014)	Petitioner
		U.S. App. No. 18/275,777 (EX2015)	Petitioner
		U.S. App. No. 18/953,525 (EX2016)	Petitioner
Hossler et. al. 2009	Vertical watermark: “Downloaded from [website] by guest on 30 March, 2020”	EP ‘466 Opposition (EX2017)	df-mp Dörries Frank- Molnia & Pohlman

⁴ Wang filed in U.S. Application No. 17/650,803 (EX2014) also bears the same
“D3” notation in the top right as Wang filed in the EP ‘466 Opposition. EX2013.

		U.S. App. No. 17/650,803 (EX2018)	Petitioner
		U.S. App. No. 18/275,777 (EX2019)	Petitioner
		U.S. App. No. 18/953,525 (EX2020)	Petitioner
Koshiha et al. 2007	Vertical watermark: “Downloaded from [website] by guest on December 18, 2014”	EP ‘466 Opposition (EX2040)	df-mp Dörries Frank- Molnia & Pohlman
		U.S. App. No. 17/650,803 (EX2041)	Petitioner
		U.S. App. No. 18/275,777	Petitioner

		(EX2042)	
		U.S. App. No. 18/953,525 (EX2043)	Petitioner
Hashiguchi et al., 2008	English machine translation of the corresponding Japanese article	EP '466 Opposition (EX2025)	df-mp Dörries Frank- Molnia & Pohlman
		U.S. App. No. 17/650,803 (EX2026) ⁵	Petitioner
		U.S. App. No. 18/275,777 (EX2044)	Petitioner

⁵ The version of Hashiguchi filed in U.S. Application No. 17/650,803 (EX2026) bears the same “D51a” notation in the top right as Hashiguchi filed in the EP '466 Opposition (EX2025).

		U.S. App. No. 18/953,525 (EX2045)	Petitioner
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Moreover, as part of the EP '466 Opposition, the Patent Owner filed a version of the Tokunaga bearing a handwritten annotation "Reference (7) – Appendix B" in the upper right-hand corner. EX2029. Notably, Petitioner here filed the *exact same* document with the same handwritten annotation as part of the prosecution history for its U.S. Patent Application Nos. 17/650,803 (EX2030); 18/275,777 (EX2031); and 18/953,525 (EX2032).

Further, the Notice of Opposition dated November 5, 2020 in the EP '466 Opposition relied upon D19, an unpublished document with no attribution that described experiments comparing the activity of *Limulus* Factor C in two HEK293 cell lines. EX2035 at 4, 7; EX2036. Figures and data from D19 were later submitted to the PTO in Petitioner's U.S. patent application number 17/650,803 filed February 11, 2022, published as U.S. Patent Application Pub. No. US 2023/0258647 on August 17, 2023. *Compare* EX2036 Figs. 1-4 with EX2021 Figs. 11-13, 15.

Taken together, this evidence strongly indicates that Petitioner filed both the EP '466 Opposition and the EP '670 Opposition, and thus sponsored the arguments and opinions made in the Notice of Opposition and Frohman Declaration submitted

in the latter. As discussed further below, the arguments made by the Opponent in the EP '670 Opposition and the Frohman Declaration and Petitioner's arguments here are directly contradictory. This conflict renders the Petitioner's unpatentability challenge exceptionally weak, and further favors discretionary denial.

b. The Opponent's arguments are directly contradictory to Petitioner's arguments here

The 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. *See* Pet. at 32 and 42 (quoting ¶¶ 07-12 of the '629 Publication).

However, the Opponent ***criticized*** these same statements from the '629 Publication as “very generic and entirely unsupported.” EX2006 ¶¶ 35, 75. The Opponent argued that “the skilled person merely had to determine the sequence of the *Limulus* Factor C protein, or cDNA sequence encoding the same, to carry out its recombinant production.” *Id.* ¶ 31. Further, the Opponent asserted that “the use of a Factor C derived from *Limulus polyphemus* is explicitly disclosed” in the '767 Application. EX2006 ¶¶ 48-51 (discussing D1).

Thus, the Opponent, which evidence indicates is Petitioner, ***agrees*** that use of *L. polyphemus* Factor C is ***explicitly disclosed*** in the '767 Application and a POSA “would not only be able to produce a *Limulus* Factor C without undue burden, but

that they would further expect the invention of [the '767 Application] to ‘*also work when Factor C is the Factor C of Limulus Polyphemus.*’” *Id.* at ¶ 50 (emphasis in original). The Opponent appears to agree with Patent Owner that “*in view of the guidance in the [‘767 Application] specification; the high level of skill in the art; and the existing knowledge in the art a person skilled in the art would readily be able to generate and use the polypeptides that are encompassed by the claims,*’ including a *Limulus* Factor C. *Id.* at ¶ 60. (emphasis in original).

In sum, the evidence indicates that Petitioner has advocated before the European Patent Office that the '767 Application (which is substantively identical to the '109 Patent specification) adequately describes and enables expression of recombinant *L. polyphemus* Factor C from mammalian cells as recited in the claims of the '109 Patent. If Petitioner is indeed the Opponent, as the evidence indicates, the Board should not rely on arguments that Petitioner repudiated less than two months before filing the Petition.

c. The Frohman Declaration provides evidence supporting discretionary denial

Regardless of the identity of the Opponent, the Frohman Declaration provides substantive support for the Director to deny institution based on the weakness of the unpatentability challenge. *See* Process Memorandum at 2.

Claim 1 of EP '670 is directed to a method for producing an endotoxin detecting agent by recombinantly expressing Factor C derived from *L. polyphemus*. EX2006 ¶¶ 8-9. The Opponent argued that this claim would be obvious because “it would have merely been a matter of **routine analysis** to obtain the sequences” of *L. polyphemus* Factor C. *Id.* ¶¶ 30-31 (emphasis in original). According to the Opponent, Professor Frohman is an expert with 38 years of experience in molecular cloning who confirmed that the inventors of EP '670 used “standard [] techniques, which were available well before the [2016] priority date, to determine the claimed Factor C sequences.” *Id.* ¶¶ 33, 35.

A few examples of where Professor Frohman offered opinions inconsistent with Petitioner's arguments in the Petition are discussed below.

Professor Frohman developed a technique called RACE (for Rapid Amplification of cDNA Ends) in 1988. EX2004 ¶ 8. He states that “[i]t would have been entirely straightforward for the skilled person to design RACE primers based on the available *Limulus* sequence information” including a 1991 publication by Tokunaga cited as D22, “and then use any of the available RACE-PCR kits to obtain the full-length cDNA sequence.” EX2004 ¶¶ 6, 10, 30-33.

Professor Frohman also opines that, alternatively, those working in the field could have followed the “very straightforward” protocol described in D23 and D24 that was used to obtain the cDNA sequence of *C. rotundicauda* Factor C to

successfully obtain the *Limulus* Factor C cDNA. *Id.* ¶¶ 11-12, 14, 16. Professor Frohman stated “there would be no reason to expect any technical difficulties for repeating this protocol for *Limulus*.” *Id.* ¶ 14.

Thus, according to Dr. Frohman, those working in the field had multiple ways of obtaining the full gene and amino acid sequence of *L. polyphemus* Factor C, the first using a technique published in 1988 and sequence information published in 1991 and the second using a straightforward protocol described in a patent and scientific publication from the mid to late 1990s.

With respect to expressing recombinant *Limulus* Factor C after obtaining the cDNA sequence, Dr. Frohman noted that “[t]he cDNA sequence of the *Limulus* Factor C is very similar to the other known species of horseshoe crabs, which had been successfully expressed in Sf9, CHO DG44 and HEK293 cells [as] shown in e.g., D1 (‘241).”⁶ EX2004 ¶ 45. “Given that these cells were able to incorporate vectors containing cDNA for *T. tridentatus* and/or *C. rotundicauda* and express the Factor C-encoding mRNAs and active Factor C proteins, there’s no reason to think that they would not be equally capable of handling the *Limulus* sequence.” *Id.* ¶ 46. Professor Frohman went on: “If I were to follow the example of D1 using the *Limulus* sequence, I would start with the cells exemplified in this disclosure and

⁶ Reference D1 is EP 2930241A1, which has the same disclosure as the ’767 Application to which the ’109 Patent claims priority. See EX2006 ¶ 51.

would not anticipate experiencing any difficulties.” *Id.* ¶ 47. Thus, Professor Frohman’s opinion is that those working in the field would have expected to be able to recombinantly express *Limulus* Factor C in at least CHO DG44 and HEK cells in view of the ’109 Patent specification.

In sum, Professor Frohman opined that there was no reason to believe that *L. polyphemus* Factor C would have been difficult to express after the cDNA sequence had been obtained through routine techniques. *Id.* ¶¶ 40, 44; *see also* EX2006 ¶ 68 (arguing that the sequence could have been obtained “within a matter of days”) (emphasis in original).

2. Inconsistent statements in Petitioner’s patents and publications

Another factor bearing on discretionary denial is that Petitioner’s arguments are inconsistent with statements from its patents and publications. For example, in U.S. Patent No. 10,473,663, a patent assigned on its face to Petitioner and filed as U.S. Application No. 12/823,506 on June 25, 2010, Petitioner defined “*Limulus* amebocyte lysate, or LAL” as “include[ing] a complete amebocyte lysate from *Limulus* polyphemus, or a fraction or component thereof, naturally derived or recombinantly produced...” EX2046 at 5:19-24. The claims of this patent are directed to methods of preparing *Limulus* amebocyte lysates—which were defined to include recombinantly produced lysates and their components—having increased

sensitivity to beta-glucans and reduced sensitivity to endotoxins. *See, e.g., id.*, claim 1. Such recombinantly produced lysates include Factor C, Factor B, and Pro-clotting enzyme. Thus, Petitioner sought and obtained claims encompassing recombinant *L. polyphemus* Factor C, Factor B and Pro-clotting enzyme based on a 2010 disclosure—over two years before the '840 JP Priority Application was filed.

U.S. Patent No. 6,391,570 is a patent assigned on its face to Petitioner claiming priority to October 9, 1997. EX2028. This patent acknowledges that amebocyte lysates for detection of bacterial endotoxin are produced from the hemolymph of any of the four species of horseshoe crab. *Id.* at 1:30-36 and 6:9-17. Petitioner stated that the endotoxin-mediated activation of the *Limulus polyphemus* amebocyte lysate “is well understood and has been thoroughly documented in the art.” *Id.* at 1:47-48 and Fig. 1.

Petitioner's arguments in the Petition based on purported differences between horseshoe crab species (*see, e.g.,* Pet. at 34-35, 43) are inconsistent with its own patents treating assays derived from different species as interchangeable and thoroughly documented. This should bear on the Director's discretion to deny institution.

B. Discretionary Denial Under 35 U.S.C. § 325(d)

The Director and the Board has discretion to deny institution under § 325(d), which provides “the Director may take into account whether, and reject the petition

or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). The § 325(d) analysis employs a two-prong framework: (i) whether the arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (ii) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of those arguments. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, No. IPR2019-01469, Paper 6 (“*Advanced Bionics*”) at 8 (P.T.A.B. Feb. 13, 2020) (precedential). Both prongs are met here.

1. The First Prong of the *Advanced Bionics* Test is Met

The first prong of the *Advanced Bionics* test is met as to Grounds 1 and 2 because the subject matter of the § 112 arguments presented by the Petition are substantially the same as those presented during prosecution of parent applications to the '109 Patent. The Petition focuses myopically on the prosecution of only the '109 Patent itself while largely ignoring the extensive consideration of § 112 issues by the *same* Examiner in connection with applications in the '109 Patent's chain of priority. *See* Pet. at 14-20. The Board has made clear that arguments presented in priority applications factor into the Section 325(d) analysis. *See, e.g., Passage Bio, Inc. v. The Trustees of the Univ. of Penn.*, No. PGR2021-00073, Paper 13 at 26 (P.T.A.B. Oct. 6, 2021) (“Having reviewed the prosecution histories, however, we find that Petitioner's arguments are the same or substantially the same as those

previously presented to the Office during the prosecution of the '218 application and the priority applications.").

The Petition mentions in passing that there was a written description rejection in one parent application and asserts that the scope and content of the claims was “markedly different” and thus the arguments are not the same or substantially similar. Pet. at 19 n.4. However, the Petition provides no analysis or explanation to support this conclusory assertion regarding the difference in claim scope and content and fails to explain how the arguments in the Petition are different from those previously considered by the Examiner.

As discussed below, the prosecution histories of applications in the '109 Patent's chain of priority reflect that the Examiner was acutely attuned to and fully considered potential written description and enablement issues with respect to the expression of recombinant Factor C proteins, which is the same ground raised in the Petition. *See* Pet. at 31.

Petitioner has presented no evidence the Examiner failed to consider the same issues with respect to the Challenged Claims generally, or with respect to recombinant Factor B and Pro-clotting enzyme proteins specifically.

a. Prosecution of U.S. 10,144,923

U.S. Patent No. 10,144,923 issued from the '767 Application and is a parent application of the '109 Patent with substantively the same specification. *See* Pet. at

8-10. In a September 16, 2016 Non-Final Rejection, the Examiner rejected the pending claims, which were “drawn to a genus of horseshoe crab Factor C polypeptides having activity of Factor C,” including recombinant proteins, for failing to comply with the written description and enablement requirements. EX2033 at 5-15. These rejections included a thorough analysis of the factors. *Id.* at 5, 10.

While maintaining other rejections in an April 13, 2017 Final Rejection, the Examiner *withdrew* the § 112 rejections after applicant amended the claims to recite a group of 4 horseshoe crab species—including *Limulus polyphemus*—because recombinant expression of these Factor C polypeptides were “well-known at the time of the invention.” *Id.* at 60. Thus, despite originally acknowledging the unpredictability in recombinantly expressing Factor C (*see id.* at 8, 12-13), the Examiner subsequently concluded the specification provided sufficient § 112 support for recombinant expression of *L. polyphemus* Factor C in Chinese hamster cells and human cells. *Id.* at 36-37 and 60. Thus, the Petition raises the very same issue—whether the specification provided adequate § 112 support for recombinant expression of *L. polyphemus* Factor C (*see Pet.* at 31-32)—that was considered by the Examiner during prosecution of this application.

Again showing his continued attention to § 112 issues, the Examiner issued another round of written description and enablement rejections on November 22,

2017. EX2033 at 93-164. The Examiner noted with respect to both grounds of rejection that, while the claims encompassed horseshoe crab proteins with amino acid substitutions, deletions, insertions, and additions, the specification disclosed only a single working example or representative species of the genus of claimed horseshoe crab Factor C polypeptides, “i.e., *Tachypleus tridentatus* Factor C... expressed in CHO DG44 cells.” *Id.* at 97, 99-100. The Examiner withdrew the enablement rejection but maintained the written description rejection after Applicant amended the claims to recite 80% or higher sequence identity to SEQ ID NO: 2 and SEQ ID NO: 4 (the amino acid sequences of *T. tridentatus* and *C. rotundicauda*, respectively). *Id.* at 119. The Examiner then withdrew the remaining written description rejection after the claims were amended to specify 90% or higher identity with those two sequences. *Id.* at 161.

The allowed claims encompass recombinant expression of *L. polyphemus* Factor C in a Chinese Hamster Ovary (CHO) DG44 cell and its use in an endotoxin assay kit. EX2033 at 140, 142-43 (claims 43 and 57).

b. Prosecution of U.S. 10,982,202

U.S. 10,982,202 issued from U.S. Patent Application No. 15/983,725, which is a parent application of the '109 Patent having substantively the same specification. *See* Pet. at 8-9. In an October 8, 2019 Non-Final Rejection, the Examiner rejected the then-pending claims for lack of written description and enablement, which again

included discussion of the relevant factors for written description and the *Wands* factors for enablement. EX2034 at 7-16. The then-pending claims were directed to methods comprising the step of recombinantly expressing the horseshoe crab Factor C in a human cell or a Chinese hamster cell as a host cell. *Id.* at 8-9. The Examiner argued the specification only disclosed two representative species: “recombinantly expressing *Carcinoscorpius rotundicauda* or *Tachypleus tridentatus* Factor C using a Chinese Hamster Ovary (CHO) cell or a human embryonic kidney (HEK) cell as an expression host.” *Id.* at 8-9, 15.

The written description rejection was maintained in a February 12, 2020 Final Rejection. EX2034 at 36-44. In the Final Rejection, the Examiner asserted the claimed genus was “widely variant” and had a high level of unpredictability with respect to a claim limitation concerning N-glycosylation of recombinant Factor C, not the underlying description of expressing the Factor C in mammalian cells. *See id.* at 41-44. Applicant amended the claims to specify the mammalian cell is CHO or HEK to overcome the written description rejection, and after additional prosecution, the Examiner allowed the amended claims. *Id.* at 89-96; *id.* at 76-81 (claim listings).

Relevant to the '109 Patent claims, allowed '202 patent claim 9 was directed to a method for producing an endotoxin assay agent comprising recombinantly expressing and secreting the horseshoe crab Factor C using a CHO or HEK host cell,

wherein the Factor C had the amino acid sequence of *L. polyphemus* Factor C. EX2034 at 91-92 (claim 9), *id.* at 94-95 (statement of reasons for allowance). Thus, the Petition raises the very same issue—whether the specification provided adequate § 112 support for recombinant expression of *L. polyphemus* Factor C (*see* Pet. at 31-32)—that was considered by the Examiner during prosecution of this application also.

c. Prosecution of U.S. 11,236,318

U.S. 11,236,318 issued from U.S. Patent Application No. 16/399,386, which is a parent application of the '109 Patent having substantively the same specification. This is the only parent application prosecution history mentioned in the Petition. Pet. at 19, n.4. In a June 30, 2020 Non-Final Rejection, the Examiner rejected the then-pending claims for indefiniteness and failure to comply with the written description requirement. EX1040 at 370-376. The rejected claims were directed to Factor C proteins having activity of Factor C with an amino acid sequence having 90% or higher sequence identity, recombinantly expressed from CHO or HEK cells and having a particular level of residual activity. EX1040 at 373-374. Although the Examiner conducted a thorough analysis of all of the relevant factors, the rejection was based in large part on the residual activity limitation, not the ability to recombinantly express Factor C. *Id.*

The § 112 rejections were withdrawn in an October 8, 2020 Final Rejection. EX1040 at 185. The Examiner acknowledged that “[a]s amended, claims 1 and 10 are drawn to a horseshoe crab Factor C protein having activity of Factor C, wherein the horseshoe crab is selected from the group consisting of *Tachypleus tridentatus*, *Limulus polyphemus*, and *Carcinoscorpius rotundicauda*, and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Chinese Hamster Ovary (CHO) DG44 cell or Human Embryonic Kidney (HEK) cell.” EX1040 at 187.

Thus, the Petition raises the very same issue—whether the specification provided adequate § 112 support for recombinant expression of *L. polyphemus* Factor C (*see* Pet. at 31-32)—that was considered by the Examiner during prosecution of this application as well.

d. Prosecution of the '109 Patent

The prosecution file history of the '109 Patent shows that the Examiner continued to consider compliance with § 112 in connection with the claims. In a September 15, 2023 Non-Final Rejection, the Examiner rejected the claims under § 112(b) and (d). EX1002 at 181-182.

While the § 112 rejections were extant, and in advance of an Applicant-Initiated Interview, the Examiner “presented a revision to the applicant’s proposed claim 1 (Appendix E) for discussion.” EX1002 at 153, 159. The revisions ***proposed***

by the Examiner included reciting that the horseshoe crab Factor C “is a *Tachypleus tridentatus* Factor C or a *Limulus polyphemus* Factor C”—one of the claim limitations that Petitioner asserts lacks adequate written description and enablement. Compare EX1002 at 160 with Pet. at 26-27, 40-41, 55.

The revisions proposed by the Examiner were adopted by applicant. EX1002 at 119-120. The Examiner then proposed additional amendments to address the remaining § 112 issues, which the applicant adopted, leading to allowance of the claims. EX1002 at 69-72.

In sum, although the Examiner did not expressly reject the Challenged Claims for lack of written description and enablement (i) he was attuned to those issues during prosecution of multiple parent applications with claims with similar limitations as the Challenged Claims; (ii) he issued § 112 rejections during prosecution of the Challenged Claims; and (iii) he proposed some of the claim limitations Petitioner now argues lack written description and enablement support. Petitioner has failed to explain how the subject matter of its § 112 arguments are *not* substantially the same as those previously presented to the Office during prosecution of the patents discussed above. Accordingly, the first prong of the *Advanced Bionics* test is met.

2. The Second Prong of the *Advanced Bionics* Test is Met

The second prong of the *Advanced Bionics* test is likewise satisfied because Petitioner has failed to demonstrate that the Examiner erred, let alone erred in a manner material to patentability, when the Examiner previously considered and rejected substantially similar arguments as Petitioner relies on here. Petitioner does not even address the lack of written description and lack of enablement arguments raised during prosecution of several family members, or the § 112 arguments raised during prosecution of the '109 Patent itself beyond a conclusory footnote. Pet. at 19 n.4. On this basis alone, the Board should deny institution. *See Vital Connect Inc. v. Bardy Diagnostics, Inc.*, No. IPR2023-00381, Paper 7 at 19-20 (P.T.A.B. July 11, 2023) (denying institution where petition is “silent on material error”).

Indeed, as the Board made clear in *Advanced Bionics*, “[i]f a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error,” then “the Director generally will exercise discretion not to institute *inter partes* review.” *Advanced Bionics* at 8-9. When analyzing the second prong, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics* at 9 (cleaned up).

VI. CONCLUSION

Patent Owner respectfully requests the Director exercise her discretion and deny institution on one or more of the grounds discussed above.

Respectfully Submitted,

Dated: May 9, 2025

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

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above, Patent Owner's Discretionary Denial Brief, complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Request, including footnotes contains 8,756 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24.

Respectfully Submitted,

Dated: May 9, 2025

/Alexander B. Stein/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on May 9, 2025, a copy of this PATENT OWNER'S DISCRETIONARY DENIAL BRIEF was served via the email correspondence address of record for Petitioner's counsel of record:

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