

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,
Petitioner,

v.

SEIKAGAKU CORPORATION,
Patent Owner.

Case No. IPR2025-00440
Patent No. 11,236,318

**PETITIONER'S OPPOSITION TO PATENT OWNER'S
DISCRETIONARY DENIAL BRIEF**

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1001	U.S. Patent No. 11,236,318 (“the ’318 patent”)
1002	Declaration of Siddhartha Jain, Ph.D., PMP (“Jain”)
1003	Curriculum Vitae of Dr. Siddhartha Jain, Ph.D., PMP
1004	Prosecution History for U.S. Application No. 16/399,386
1005	International Patent Publication No. WO 2018/074498 A1
1006	U.S. Patent Application No. 14/650,767, as filed June 9, 2015
1007	Muta et al., “Limulus Factor C. An endotoxin-sensitive serine protease zymogen with a mosaic structure of complement-like, epidermal growth factor-like, and lectin-like domains,” <i>J Biol Chem.</i> 1991 Apr 5; 266(10):6554-61.
1008	Gan et al., “Analysis of Protein Sequence/Structure Similarity Relationships,” <i>Biophys J.</i> 2002 Nov; 83(5):2781-91.
1009	U.S. Patent Application Publication No. 2015/0307864
1010	Karen McClymont, Ph.D. Thesis, submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy from the University of Glasgow, Institute of Molecular, Cell and Systems Biology College of Medical, Veterinary and Life Sciences, March 2017.
1011	Transition Certification for U.S. Patent Application No. 15/983,725, filed May 31, 2019.
1012	U.S. Patent No. 5,716,834
1013	Declaration of Dr. Mary K. Bolin
1014	U.S. Patent No. 5,858,706
1015	International Patent Publication No. WO 2000/026366 A1
1016	Iwanaga, Sadaaki, “Biochemical principle of <i>Limulus</i> test for detecting bacterial endotoxins,” <i>Proc. Jpn. Acad., Ser. B. Phys Biol Sci.</i> 2007 May; 83(4):110-9.
1017	RESERVED
1018	RESERVED
1019	Japanese Priority Document JP2012-269840 (certified translation, plus original)
1020	U.S. Application No. 14/650,767, addition to PCT specification
1021	Higdon, R. et al., “Modeling sequence and function similarity between proteins for protein functional annotation,” <i>Proc Int Symp High Perform Distrib Comput</i> ; 2010: 499–502.

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1022	Tokunaga, F., et al. “Further studies on lipopolysaccharide-sensitive serine protease zymogen (Factor C): Its isolation from <i>Limulus polyphemus</i> hemocytes and identification as an intracellular zymogen activated by α -chymotrypsin, not by trypsin,” <i>J. Biochem.</i> 1991 Jan; 109(1):150-7.
1023	Levin, J., Bang, F., “The role of endotoxin in the extracellular coagulation of <i>Limulus</i> blood,” <i>Bulletin of John’s Hopkins Hospital.</i> 1964 Sep: 115:265-74.
1024	Walls, E. et al, The Horseshoe Crab, <i>Limulus polyphemus</i> : 200 Million Years of Existence, 100 Years of Study, <i>Reviews in Fisheries Science.</i> 2002; 10(1):39-73.
1025	Carmichael, R., et al., “Changing Global Perspectives on Horseshoe Crab Biology, Conservation, and Management,” Springer, Ch. 29: “Biotechnology Efforts to Conserve Horseshoe Crabs Through the Development of Recombinant Factor C-Based Endotoxin Test” pp. 501-512 (2015).
1026	Dwarakanath et al., “Recombinant COS-1 cells express <i>Carcinoscorpius rotundicauda</i> Factor C,” <i>Biotechnology Letters.</i> 1997 April; 19(4):357-361.
1027	Wang, J. et al., “Functional expression of full length <i>Limulus</i> Factor C in stably transformed Sf9 cells,” <i>Biotechnology Letters.</i> 2001; 23:71-76.
1028	Ding et al, “A new era in pyrogen testing,” <i>Trends in Biotechnology.</i> 2001 Aug; 19(8):277-81.
1029	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Declaration Under 37 C.F.R. § 1.132, Feb. 22, 2018.
1030	Barrabes, S. et al., “Effect of sialic acid content on glycoprotein p/ analyzed by two-dimensional electrophoresis,” <i>Electrophoresis.</i> 2010 Sep; 31(17):2903-12.
1031	Palomares, L.A., “Production of Recombinant Proteins: Challenges and Solutions,” From: <i>Methods in Molecular Biology</i> , vol. 267: <i>Recombinant Gene Expression: Reviews and Protocols</i> , Second Edition Edited by: P. Balbás and A. Lorence © 2004 Humana Press Inc., Totowa, NJ, pp. 15-51
1032	U.S. Patent No. 6,645,724
1033	Mizumura, H., et al., “Genetic engineering approach to develop next-generation reagents for endotoxin quantification,” <i>Innate Immunity.</i> 2017 Feb; 23(2):136-146.

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1034	Ding et al., “Expression of full length and deletion homologues of <i>Carcinoscorpius rotundicauda</i> Factor C in <i>Saccharomyces cerevisiae</i> : immunoreactivity and endotoxin binding,” <i>Journal of Endotoxin Research</i> . 1997; 4(1): 33-43.
1035	International Patent Publication No. WO 2014/092079 A1 (“the ‘082 PCT”)
1036	Wang et al., “Modular Arrangement and Secretion of a Multidomain Serine Protease,” <i>J Biol Chem</i> . 2002 Sep 27; 277(39):36363-72.
1037	Marengo-Rowe, Alain, J., “Structure-function relations of human hemoglobins,” <i>Proc (Bayl Univ Med Cent)</i> 2006 Jul; 19(3):239–245.
1038	Sekiguchi, K. and Shuster, C.N., “Limits on the Global Distribution of Horseshoe Crabs (Limulacea): Lessons Learned from Two Lifetimes of Observations: Asia and America,” <i>Biology and Conservation of Horseshoe Crabs</i> , 2009.
1039	Hossler et al., “Optimal and consistent protein glycosylation in mammalian cell culture,” <i>Glycobiology</i> . 2009 Sep; 19(9):936-4.
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1042	U.S. Appln. No.: 17/554,128, “Novel Recombinant Factor C And Method for Producing the Same, and Method for Measuring Endotoxin” Non-Final Office Action, Mar. 20, 2025 (“128 App. NFR”)
1043	European Patent No. 3530670, “Method for producing endotoxin detecting agent comprising recombinant limulus factor c and use thereof,” Response to Opposition, May 9, 2025
1044	European Patent No. 3441466, “Method for Producing a Novel Recombinant Factor C, Method for Mitigating Reaction Inhibition In Endotoxin Assays, And Method for Measuring Endotoxin,” Decision on Opposition, Oct. 26, 2022
1045	USP, General Chapter Prospectus: Use of Recombinant Reagents in Bacterial Endotoxins Test. May 29, 2020
1046	Stewart, C.M., “Interim Processes for PTAB Workload Management,” Memorandum dated March 26, 2025
1047	U.S. Appln. No.: 17/554,128, “Novel Recombinant Factor C And Method for Producing the Same, and Method for Measuring Endotoxin” Amendment under 37 C.F.R. § 1.111 , Jan. 28, 2025
1048	European Patent No. 3530670, “Method for producing endotoxin detecting agent comprising recombinant limulus factor c and use thereof,” Notice of Opposition, Nov. 22, 2024

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1049	RESERVED
1050	U.S. Appln. No.: 16/331,810, “Recombinant Proteins Derived From Genus Limulus, and DNA Molecules Encoding Same,” Notice of Abandonment, Mar. 14, 2023
1051	Press Release, “USP Provides Guidance on the Use of Recombinant Reagents for the Bacterial Endotoxin Test” May 29, 2020
1052	U.S. Patent Application Publication No. 2019/0241629 (“629 publication”)
1053	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Non-Final Office Action, Sept. 16, 2016
1054	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Final Office Action, Apr. 13, 2017
1055	U.S. Appln. No.: 14/650,767, “Novel Recombination Factor C and Method for Producing the Same, and Method for Measuring Endotoxin,” Amendment under 37 C.F.R. § 1.111 , Mar. 16, 2017

I. INTRODUCTION

During prosecution of U.S Patent No. 11,236,318 (“the ’318 Patent”), Patent Owner faced a written description rejection that prompted amendment of all of its pending claims to narrow the scope of the originally claimed genus. In response to that amendment, the Examiner withdrew the written description rejection. In the same prosecution history, years later, Patent Owner reintroduced a claim that stripped out this amendment. The Examiner didn’t notice that this claim lacked support and an enabling disclosure. Charles River Laboratories, Inc. (“CRL” or “Petitioner”) has petitioned for institution of *inter partes* review of **only claim 21** of the ’318 Patent (directed to recombinantly produced Factor C from the horseshoe crab *Limulus polyphemus*) because that claim was erroneously granted at the very end of nearly two and a half years of prosecution and claims recombinant horseshoe crab proteins that the inventors themselves admitted in a separate patent filing **were not in their possession** as of the claimed priority date of the ’318 Patent. Charles River has intentionally challenged **only** this one unpatentable claim in order to focus the Board’s resources on this clear error and to resolve this erroneous allowance in an efficient and expedient manner.

Notably, the agency has recognized this written description and enablement deficiency with claim 21 in more recent filings in the same patent family. Two months ago, the **same Examiner** who allowed challenged claim 21 and a number

of other patents in the continuity chain of the '318 Patent, rejected similar claims based on the same priority defect argument advanced in the Petition (Paper No. 2, "Pet."). EX1042, 2-3. This not only demonstrates that the Examiner's earlier allowance of claim 21 was plain mistake but it spotlights the merit of the Petition's arguments. Patent Owner's argument that the Examiner's prior consideration of §112(a) issues of later amended claims during prosecution of the '318 Patent and ancestor family member patents warrants discretionary denial should be rejected for what it is — a second attempt to slip one past the goalie.

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 even 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 the recombinant proteins of claim 21 were not obvious by October 18, 2016, Patent Owner certainly ***did not*** have possession of them by the December 10, 2012 claimed priority date of the '318 Patent. 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 challenged claim 21. 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.” EX1045, EX1051. The subject matter of claim 21 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 claim 21 was 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 claim 21’s patentability. Otherwise, this improvidently granted claim will allow Patent Owner to stand in the way of 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 IPR20024-0440 against claim 21 of the ’318 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 on 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 claim 21 recites:

21. A horseshoe crab Factor C protein having activity of Factor C¹, wherein the horseshoe crab is *Limulus polyphemus*, and

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

wherein the Factor C protein exhibits a residual activity of at least one selected from the group consisting of:

(1) 10% or higher in the presence of 21 mM sodium citrate; and

¹ The ’318 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, 15:37-42.

(2) 15% or higher in the presence of 16 mM magnesium sulfate.

Claim 21 is not involved in any other *inter partes* review proceedings or parallel district court litigation. However, pending claims in a child application to the '318 Patent requiring recombinant *Limulus polyphemus* Factor C have very recently been rejected for nearly identical priority claim breaking arguments (and application of intervening prior art) as those made in the Petition. In addition, claims similar to claim 21 have been pursued by Patent Owner in Europe and have been revoked (or argued patentable by Patent Owner itself in conflict with its arguments for patentability here) based on arguments consistent with those advanced in this Petition. These prior adjudications warrant careful consideration of the merits of Petitioner's challenge to claim 21.

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 '318 Patent and was filed on Dec. 17, 2021 (claiming priority to the same Japanese priority document (JP 2012-269840), filed on Dec. 10, 2012).

Currently pending representative independent claim (claim 3) of the '128 Application recites (bolded text overlaps with challenged claim 21):

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 substrate for the Pro-clotting enzyme protein,

wherein the horseshoe crab is *Limulus polyphemus*,

wherein the Factor C protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,

wherein the Factor B protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,

wherein the Pro-clotting enzyme protein is produced through being recombinantly expressed from a Human Embryonic Kidney (HEK) 293 cell,

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.

EX1047, 4-5.²

On March 20, 2025, the Examiner (the *same* Examiner who previously examined challenged claim 21 of the '318 Patent, *and* its grandparent '767 Application), issued a Non-Final Rejection finally denying the pending claims' 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/JP2013/083082 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*

² Unless otherwise noted, all emphasis is added and internal citations and quotations are omitted.

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 both Mizumura (WO 2018/074498), relied on in Ground 1 of the Petition, where the ’318 Patent inventors admitted to purportedly inventing recombinant *Limulus polyphemus* Factor C many years ***after*** the priority date of challenged claim 21) and McClymont (relied upon in Ground 2 of the Petition), the Examiner of the ’128 Application concluded: “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.***” EX1042, 6.

As discussed in Section III.B., *infra*, regarding material error, the Examiner of the '318 Patent and its ancestors going back to the '767 Application never recognized this deficiency in the priority claim of this patent and failed to reject pending claims accordingly. Now, nearly a decade later, that same Examiner has recognized this flaw, has articulated this defect in the prosecution of claims directed to recombinant Factor C from *Limulus polyphemus* horseshoe crabs, and has rejected those claims based on intervening prior art. EX1042, 2-6.

It is incumbent on this Board to carefully examine challenged claim 21 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 patent 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 '318 Patent and contains a different specification. The EP670 Opposition seeks revocation of Claim 1 which recites:

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.

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.,” 23), 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, ¶29. Patent Owner argues that

such argument somehow contradicts the Petition and that the contradiction supports discretionary denial. Br., 22-23.

But no contradiction exists. First, EP670 and the '318 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 '318 Patent did not, possess sufficiently to describe, or enable this invention (as they themselves admitted) as of December 10, 2012. *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 *Tachyplesus 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 ’318 Patent inventors certainly did not describe it in sufficient detail to be in possession of such an advance as of December 10, 2012. 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 an improper priority claim as to the ’318 Patent and the unpatentability of challenged claim 21 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 ’318 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 claim 21):

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, 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. Notably, the revoked claims included the limitation, “wherein the thus-expressed horseshoe crab Factor C ... 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.” EX1044, ¶6.1. The *absence* of this limitation in challenged claim 21—referred to herein and in

the Petition as the “greater sialic acid limitation”—is among the reasons Petitioner argues this claim was allowed in error. *See* Section III.B., Pet. 17-18. However, this limitation was included in the subject claims of the EP466 Opposition and those claims were *still* found to be unsupported by the disclosure shared with the ’318 Patent. EX1044, ¶8.1.

Moreover, 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 common specification to disclose features shared by the opposed claims in Europe and challenged claim 21 warrants a close examination of that claim and consideration of the Petition’s merits.

B. Response to Patent Owner’s Remaining Assertions Regarding “Additional Discretionary Denial Factors”

None of Patent Owner’s arguments regarding the applicability of so called “additional factors” weigh in favor of discretionary denial.

1. The Lack of Settled Expectations of the Parties And Efficiency Considerations Weigh In Favor of Institution.

As Patent Owner notes, the ’318 Patent issued less than three years prior to the filing of the Petition. This is a very short period of time relative to the life of the patent, particularly considering that *inter partes* review can only be brought after the expiry of nine months *after* patent issuance. 35 U.S.C. §311(c)(1). The

instant IPR was filed in conjunction with a PGR (PGR2025-00023) because as Petitioner has uncovered the overreach as to Patent Owner's claim scope compared with its priority disclosures, discussed in both Petitions, it has moved quickly to bring the same to the Board's attention.

There was no delay on Petitioner's part in deciding to bring, in preparing, and in filing the Petition. Patent Owner fails to offer any evidence (or even argument) that Patent Owner took steps in reliance on its exclusive rights conferred by claim 21, or made any investments, or engaged in any other activities based on its settled expectations regarding claim 21, that would lead to Patent Owner's harm or detriment if that claim were found unpatentable. As noted above, related pending claims are being rejected by the same Examiner on grounds nearly identical to those advanced by the Petition. A patent owner cannot have reasonable "settled expectations" as to the validity of a particular claim if comparable claims are being rejected by the PTO at the same time. EX1046, 2.

Further, and as noted above, the fact that the Petition challenges *only* claim 21 weighs against discretionary denial. Petitioner was surgical in assessing the unpatentability of this claim in view of the weight of the evidence presented in the Petition and the strength of the merits in favor of unpatentability. The Board need only consider such evidence as it relates to a single claim, and such can be done efficiently and without delay. To credit Patent Owner's logic (Br., 21), on the

other hand, would be tantamount to incentivizing potential challengers to attack many claims even when only some are (or one is) material.

2. The Petition's Provision Of Helpful Expert Testimony Weighs Against Discretionary Denial.

The Petition's reliance on expert testimony, if anything, counsels *against* discretionary denial. The Declaration of Dr. Siddhartha Jain ("Jain") provides the required scope and content of the art as context for precisely why Patent Owner did not have possession of (and did not enable the full scope of) the subject matter of claim 21 as of the earliest claimed priority date of that application. EX1002, ¶¶72-146. As noted above, the same Examiner who examined claim 21 has now come to recognize this same priority flaw and has made the very same argument in rejecting similar pending claims. EX1042, 3-4. Dr. Jain's testimony provides helpful technical explanation for the Board's assessment of this specific challenge to this specific claim and its potential arrival at the same conclusion.

In addition, as discussed in the Petition, the inventors of claim 21 admitted years after the alleged priority date for that claim that they only *later* came to possess the sequence information for *Limulus polyphemus* Factor C and the ability to recombinantly express the same. EX1005, ¶¶ 2-17, 49-75, 194-195, (SEQ ID NOS. 1-4). That the Petition relies on (and Dr. Jain provides) a POSAs explanation of that admission simply completes the public record (that is, the same conclusion reached by both Parties). EX1002, ¶¶72-146. Dr. Jain's testimony does

not fill gaps in the art (and Patent Owner identifies no such gaps), but merely confirms what the inventors (and POSAs) already knew, and stated publicly, to be true. *Id.*; *iRhythm Technologies, Inc. v. Welch Allyn, Inc.*, Paper No. 10, 2-3 (PTAB Jun. 6, 2025). This weighs against discretionary denial.

Patent Owner argues that the Petition should be discretionarily denied because it lodges a priority attack, but it is well settled that the Board may assess the '318 Patent's priority claim before then considering applicable prior art. *SAP v. Arunachalam*, IPR2014-00414, Paper 24 at 21 (PTAB Aug. 17, 2015); *FedEx v. IpVenture*, IPR2014-00833, Paper 14 at 20-22 (PTAB Dec. 3, 2014); *see also* PTAB Consolidated Trial Practice Guide, November 2019, 59.

3. Arguments Advanced in the EP670 Opposition Are Consistent With And Support Institution of the Petition.

Finally, Patent Owner argues that “[w]eaknesses in Petitioner’s unpatentability challenge also support discretionary denial” and cites to supposed contradictory positions purportedly advanced in the EP670 Opposition. Br., 22-23.³ As discussed in Section II.A.2., *supra*, the obviousness-type arguments made

³ While entirely immaterial to the Director’s review, Patent Owner 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

in EP670 Opposition do not contradict the written description and 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

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 (or were cited in the EP466 Opposition) were filed publicly in connection with those Oppositions and were available online from the European 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 an *inter partes* review challenge to claim 21 of the '318 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*, IPR2022-00318, 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.”).

standards, and in view of the guidance provided in the distinct specification of the EP670) for a POSA to use the EP670 claimed method to recombinantly produce *Limulus polyphemus* horseshoe crab Factor C.⁵ By contrast, Dr. Frohman provided no opinion, evidence, or other testimony relating to whether Applicant described or enabled the recombinant proteins of claim 21 based on the disclosures provided in the specification of a ***different patent*** (the '318 Patent priority disclosures, which are 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—by December 12, 2010, a POSA would have had to conduct undue experimentation to discover and characterize the gene and amino acid sequence for *Limulus polyphemus* Factor C and recombinantly express it in HEK293 cells. *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

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 publication of the '318 Patent's grandparent application (App. No. 14/650,767). Patent Owner abandoned that application. EX1050.

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.”).

The Opponent’s arguments and expert testimony in EP670 do not contradict the Grounds of the Petition and therefore do not support discretionary denial.

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. EX1046, 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 ’318 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, 1:25-67. 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 claim 21 is directed to a recombinantly produced Factor C protein that has the endotoxin detecting ability of native Factor C but is generated in a laboratory without the need to harvest lysate directly from horseshoe crabs. EX1001, cl. 21.

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.” EX1045, EX1051. 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 synthetic alternatives. The public has an interest in the advancement of this transition (and advancement of 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 claim 21, which issued on February 1, 2022 (based on an earliest claimed priority date of December 10, 2012) will prevent would-be competitors from developing recombinant *Limulus polyphemus* Factor C proteins for another decade and will hinder the regulatory and public health transition from “using animal-derived materials to synthetic and recombinant materials.” EX1045; EX1051. Accordingly, the public has a strong interest in the Board’s careful review of the patentability of claim 21.

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).

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

The Grounds (1 and 2) of the Petition argue that the alleged priority documents do not support a claim to the genus of Factor C proteins encompassed

by claim 21 and that intervening art⁶ between the incorrect priority date and actual filing date is applicable and renders that claim unpatentable. *See* Pet. Sections IX and XI. These arguments were never previously presented to the Office or considered by the Examiner. Thus, the first prong of *Advanced Bionics* is not met.

As the Petition and Patent Owner acknowledge, a rejection based on 35 U.S.C. § 112 for inadequate written description support was lodged during prosecution of the '318 Patent. But Patent Owner's sweeping allegation that "Petitioner's Section 112 arguments ... are substantially the same as those the PTO considered during prosecution" (Br., 11) ignores: (1) the significant differences between the previously rejected claims and challenged claim 21, and (2) the claim amendments Patent Owner made to overcome those rejections that were stripped from claim 21 when it was presented years later. In view of these significant differences, the Examiner did not consider sufficiency under § 112 with respect to the particular scope of challenged claim 21. If any such consideration was made,

⁶ The prior art cited in the Grounds—Mizumura, the '498 PCT, and McClymont—were not of record nor cited nor applied during prosecution of the '318 Patent, where the Examiner made no substantive determination about whether the '318 patent was entitled to an earliest effective filing date of December 10, 2012. *See e.g.*, EX1004, 369.

then the Examiner's conclusion constituted material error as explained in Section III.B., *infra*.

1. Patent Owner's Comparison of the Rejected Claims and Challenged Claim 21 is Incomplete

On page 12 of its Brief, Patent Owner compares pending claims 2 and 8, which were rejected for lack of adequate written description, with challenged claim 21. In an effort to paint these claims as similar, Patent Owner color codes similar wording between the claims but glosses over a critical difference in their scope. Claim 2 is directed to recombinant Factor C protein having an amino acid sequence of SEQ ID NO 2, SEQ ID NO 4, or an amino acid sequence having 90% or higher sequence identity to either of these two sequences. As the '318 Patent describes, SEQ ID NO 2 is the amino acid sequence for the Japanese species of horseshoe crab (*Tachypleus tridentatus*), and SEQ ID NO 4 is the amino acid sequence for the Singaporean species of horseshoe crab (*Carcinoscorpius rotundicauda*). EX1001, 40:5-15. Thus, pending claim 2 attempted to cover not only recombinant proteins with sequences that had been known to correspond to the Japanese and Singaporean horseshoe crabs, but ***any sequence variations*** of these so long as the sequences shared 90% identity with SEQ ID NOS 2 or 4.

As highlighted in the Petition, as of the date of the '318 Patent's most fulsome priority disclosure (December 10, 2013), it is undisputed that the amino acid sequence for a different species of horseshoe crab, *Limulus polyphemus*, was

not yet known (and therefore was not known to fall within or without the 90% sequence identity range set forth in the claims). Pet. 20-42. Given the extraordinary breadth of the genus of possible sequences covered by pending claim 2 (and the equally large number of proteins they could encode), the Examiner rightly rejected claim 2 for lack of adequate written description. EX1004, 371-376.

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.” EX1004 (’318 FH), 376. The Examiner also found that “Other 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.*, 376. Of course, the fact that the amino acid sequence for Factor C from *Limulus polyphemus* horseshoe crabs was possibly somewhere in that 90% sequence identity range (but was unknown to a POSA as of December 10, 2013) did not impact the Examiner’s § 112 rejection.

2. Applicant’s Amendment Narrowed the Pending Claim And The §112 Rejection Was Withdrawn

In addressing this rejection, Patent Owner amended claim 2 to limit *all of the sequence limitations* to the case where 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 [of *Tachypleus tridentatus* or *Carcinoscorpius rotundicauda*] and/or a corresponding horseshoe crab Factor C protein recombinantly expressed using Sf9 as a host cell” (“the greater sialic acid limitation”):

2. (currently amended): A Factor C protein 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 Human Embryonic Kidney (HEK) cell, and wherein the expressed Factor C protein comprises an amino acid sequence selected from the group consisting of:

(A) the amino acid sequence of SEQ ID NO: 2, and 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 of *Tachypleus tridentatus* and/or a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell;

(B) an amino acid sequence having 90% or higher sequence identity to the amino acid sequence SEQ ID NO: 2, and having activity of Factor C, and 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 of *Tachypleus tridentatus* and/or a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell;

(C) the amino acid sequence of SEQ ID NO: 4, and 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 or *Carcinoscorpius rotundicuada* and/or a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell; 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, and 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 of *Carcinoscorpius rotundicuada* and/or a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell, and

~~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 at least one selected from the group consisting of:

- (1) 10% or higher in the presence of 21 mM sodium citrate,
- (2) 25% or higher in the presence of 52 mM sodium hydrogen carbonate;
- (3) 25% or higher in the presence of 214 mM sodium chloride;
- (4) 15% or higher in the presence of 16 mM magnesium sulfate.

EX1004, 227-28.

Subsequent to the Patent Owner's amendment to include the greater sialic acid limitation to each sequence limitation of the pending claim, the Examiner withdrew the written description requirement and focused instead on the obviousness of the pending claims. EX1004, 183-203, 99-116. All of the subsequent new and amended claims contained the greater sialic acid limitation (*id.* at 227-31, 168-73) until the August 24, 2021 amendment, in which new claim

24 (identical to challenged claim 21) was introduced without the greater sialic acid limitation. *Id.* at 73.

While Patent Owner presented arguments and data purportedly showing unexpected results with respect to claim 24, there was no consideration of whether Patent Owner sufficiently described the full scope of such claim as of December 10, 2012. Indeed, the weight of the evidence demonstrates otherwise:

- The data that Dr. Mizumura submitted purporting to show such unexpected results was contemporaneously generated on or around August of 2021 and provides no evidence that the inventors possessed recombinant Factor C protein in 2013. EX1004, 149-153. *Billups-Rothenberg, Inc. v. Associated Reg'l and Univ. Pathologists*, 642 F.3d 1031, 1037 (Fed. Cir. 2011) (“[Patentee] cannot satisfy the written description requirement merely through references to later-acquired knowledge.”); *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1342-44 (Fed. Cir. 2021) (no written description—“[E]vidence illuminating the state of the art subsequent to the priority date is not relevant to written description”).
- The data that Dr. Mizumura submitted earlier in prosecution to report to the Examiner that the amino acid sequence of *Limulus polyphemus* Factor C protein has 90.8 or 91.8 percent sequence identity with *Carcinoscorpius rotundicuada* and *Tachypleus tridentatus*, respectively, was based on the

then-recent and newly completed sequencing of *Limulus polyphemus*

proteins as reported in the August 8, 2019 publication of US2019/0241629, which Dr. Mizumura attached to his declaration. EX1004, 243-248, 294-338.⁷ By Dr. Mizumura's own admission in US2019/0241629, the *Limulus polyphemus* Factor C amino acid sequence had not been completed back in 2012 when Patent Owner filed the priority document for the '318 Patent:

[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...

The present inventors were successful in the acquisition of full-length cDNAs encoding all protein factors involved in the clotting mechanism of *Limulus polyphemus* which no one had ever been successful for a long time, and the expression of all recombinant proteins thereof, and further found that these can

⁷ The specification of US2019/0241629 is identical to WO2018/074498 A1 (cited as prior art in Ground 1 of the Petition).

be utilized in various applications, and ***thus completed the present invention.***

EX1052, ¶¶12, 25.

The Petition does not rehash the written description arguments made by the Examiner with respect to pending claim 2 because that claim was directed to a genus including recombinant Factor C of two known and disclosed species of horseshoe crabs (Tt and Cr) plus an exceedingly broad array of additional sequences (known and unknown). Claim 21, by contrast, is a claim directed to recombinant Factor C from *Limulus polyphemus* horseshoe crabs, claiming priority to a date where the Factor C amino acid for this species was undisputedly ***unknown***, and where, unsurprisingly, not a single example from such a claim was disclosed in the specification. The Examiner ***never*** considered written description support for a claim for which zero representative species were disclosed in the specification. Where the Examiner considered sufficient support for a different claim for which two representative species were disclosed, the Examiner ***still*** rightly rejected that claim. EX1004, 375-76.

Moreover, as noted above, the amendments to claim 2 were made to overcome a § 112(a) Rejection, as Patent Owner explained in its September 17, 2020 Amendment and Argument/Remarks: “At page 4 of the Office Action, claims 2-9, 12 and 13 are rejected under 35 U.S.C. § 112(a) as failing to comply with the

written description requirement. Claim 2 has been amended to incorporate the subject matter of claim 11. Claim 11 is not subject to this rejection. Accordingly, reconsideration and withdrawal of the § 112(a) rejection are respectfully requested.” *Id.* at 234. Pending claim 11 at the time included the greater sialic acid limitation:

11. The Factor C protein according to claim 2, which 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 517.

While the Examiner did not explicitly state that the §112(a) rejection was withdrawn because of such amendment, the §112(a) rejection was, in fact, withdrawn in the next Office Action, while an obviousness rejection was maintained. *Id.* at 183-203. It is not speculation to accept that the argument made explicitly in support of withdrawal of a § 112(a) rejection was acquiesced to when that rejection was, in fact, withdrawn. In any case, the fact that Patent Owner solved its §112(a) rejection problem by amending the claims to recite the greater sialic acid limitation is irrelevant to whether the Examiner ever considered a §112(a) deficiency with respect to claims injected later which stripped out that limitation but claimed recombinant proteins the inventors admittedly had not and

could not have created. And even if the Examiner did consider pending claim 24 against the requirements of §112(a), the allowance of such claims was material error as discussed in Section III.B., *infra*.

3. Applicant Did Not Face The Same or Substantially Similar Arguments as Those in the Petition in Prosecuting the '767 Application Grandparent Case.

Patent Owner also points to prosecution of the grandparent application to the '318 Patent (App. No. 14/650,767) 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 claim 21. Br., 15-18. But discretionary denial should not be wielded simply because Patent Owner can find an extraordinarily broad original claim that happened to draw an unrelated §112(a) rejection nearly five 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, Patent Owner's table on page 16-17 of its Brief demonstrates why discretionary denial should not flow from the fact that the Examiner made §112(a) rejections during prosecution of the '767 Application. Original claim 43 recites "A horseshoe crab Factor C having activity of Factor C." 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.

EX1053, 8.

Challenged claim 21, as depicted in Patent Owner's table, is significantly different from claim 47 in that it is directed to, *inter alia*, **recombinantly produced** Factor C, specifies an expression system, and includes a residual activity threshold relating to magnesium sulfate. Contrary to Patent Owner's assertion (Br., 17), the Petition does not "rehash[] substantially the same written description arguments here." The Examiner correctly found the exceedingly broad claim 43 to be insufficiently supported by the disclosure of a few examples falling within this broad scope in the specification. EX100X ('767 App. NFR), 8. The Petition, by

contrast, asserts that a claim to recombinant *Limulus polyphemus* Factor C proteins cannot be supported by the ***absence of any disclosure or examples*** whatsoever of the same, particularly where the lead inventor himself argued to the Patent Office ***years later*** that only then had he “completed the invention” underlying that claim. Examiner’s written description rejections of claims 43 and 47 of the ’767 Application are not substantially similar to the Grounds of the Petition.

The Examiner’s enablement rejection of claims 43 and 47 is likewise not substantially similar to the Grounds of the Petition. Again, the Examiner found that in view of “the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the state of the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.” EX1053, 13. As to pending claims 43 and 47, the specification provided a limited (though insufficient) number of working examples within this exceedingly broad scope. *Id.* 13-14.

Challenged claim 21, by contrast, is of a different scope and the relevant priority disclosure provides no examples at all in view of the fact that the *Limulus polyphemus* Factor C nucleic acid and amino acid sequences had not yet been elucidated. Pet. 5-6, 36. The correct but distinct written description and enablement rejections against exceedingly broad claims 43 and 47 as filed in claim 21’s

grandparent application do not warrant the Board's exercise of its discretion to deny institution of *inter partes* review or claim 21.⁸

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

1. The Examiner Erred By Allowing Claim 21 Without The Greater Sialic Acid Limitation And Based On Later Arising Data of Unexpected Results.

Patent Owner argues that there is no evidence of material error where the Examiner “previously considered and rejected substantially the same arguments as Petitioner raises here.” Br., 18. As discussed in Section III.A. *supra*, the Examiner did not consider substantially the same arguments advanced in the Grounds so Petitioner need not demonstrate material error as to either the § 112(a) rejection in

⁸ In response, as with claim 2 in prosecution of the '318 Patent, Patent Owner amended claim 43 to include the greater sialic acid limitation and requested withdrawal of the pending written description and enablement rejections. EX1055, 3. The Examiner withdrew the § 112(a) rejection citing, *inter alia*, the fact that “it was well-known in the prior art at the time of the invention that different cell types ... add sialic acid using an α -2,3 linkage”). EX1054, 6.

the prosecution of the '318 Patent or the '767 Application.⁹ But even were the arguments in the Petition deemed substantially similar to the § 112(a) rejections of the far different claims early in the prosecution of the '318 Patent or during prosecution of as-filed claims in its grandparent application, the key point is that the Examiner **did not reject such arguments**. To the contrary, the Examiner correctly lodged these rejections. EX1004, 371-76; EX1053, 3-14. The error arose because Patent Owner amended the then-pending claims¹⁰ to overcome these correct rejections but later snuck in a claim ***without*** such amended content much later in prosecution when the focus was on the obviousness of such claims and not on whether such claims enjoyed support from their alleged priority disclosures. Indeed, by the time claim 24 was introduced in prosecution—and as Patent Owner concedes (Br., 9), the focus of both the Examiner and Patent Owner was on the

⁹ Neither *Ivantis* nor *Vital Connect* (Br., 18-19) involved the question of whether allowance of claims in a grandchild application constituted material error in view of a § 112(a) rejection lodged against as-filed grandparent claims of a different scope nearly six and a half years earlier.

¹⁰ The greater sialic acid limitation was included or added to every single claim in the '767 Application (issuing as US Patent No. 10,144,923) and every single claim in the '318 Patent (except, of course, claim 21).

obviousness of the pending claims and Patent Owner’s efforts were to show that it claims demonstrated some unexpected results worthy of a patent grant. EX1004, 67-87, 95, 102-116. But as the Petition argues, such information could not have formed the basis for any determination by the Examiner that claim 24 was adequately described because the declaration provided data of purported unexpected results generated long after the asserted priority date of the ’318 Patent. *Billups-Rothenberg, Inc.*, 642 F.3d at 1037 (“[Patentee] cannot satisfy the written description requirement merely through references to later-acquired knowledge.”); *Biogen*, 18 F.4th at 1342-44 (no written description—“[E]vidence illuminating the state of the art subsequent to the priority date is not relevant to written description”).

The Examiner’s allowance of such claims in view of this data without the amendments that previously overcame the § 112(a) rejections, and in the absence of any other argument as to why such claims no longer lacked written description support, constitutes material error.

2. The Examiner’s Rejection of Similar Claims Based on Arguments From the Petition Demonstrates the Material Error in Allowing Claim 21.

The Examiner materially erred in affording claim 21 the benefit of the earliest claimed priority date of the ’318 Patent (December 10, 2012). We know this now because that very same Examiner has rejected pending claims directed to

recombinant *Limulus polyphemus* Factor C proteins based on intervening prior art available because that Examiner has determined that “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 HED 293 cell. EX1042, 4. The Examiner concluded, therefore, that such claims “are not entitled to the benefit of the priority applications 14/650,767 and PCT/JP2013/083082.” *Id.*, 2-6. The Examiner’s failure to recognize this defect during prosecution of challenged claim 21 constitutes material error weighing heavily against discretionary denial.

IV. CONCLUSION

For at least the foregoing reasons, Petitioner respectfully requests that the Board decline to exercise its discretion in denying institution and instead refer consideration to the merits panel for further review.

Respectfully submitted,
Charles River Laboratories, Inc.

Date: June 11, 2025

/Scott A. McKeown/
Scott A. McKeown, Reg. No. 42,866
WOLF, GREENFIELD & SACKS, P.C

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 8,782 words excluding; a table of
contents, a table of authorities, a certificate of service or word count, or appendix
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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:

Alexander B. Stein
Christopher J. Betti

alexander.stein@morganlewis.com
christopher.betti@morganlewis.com
Seikagaku-CR-IPR-PGR@morganlewis.com

Date: June 11, 2025

/MacAulay Rush/
MacAulay Rush
Paralegal
WOLF, GREENFIELD & SACKS, P.C.